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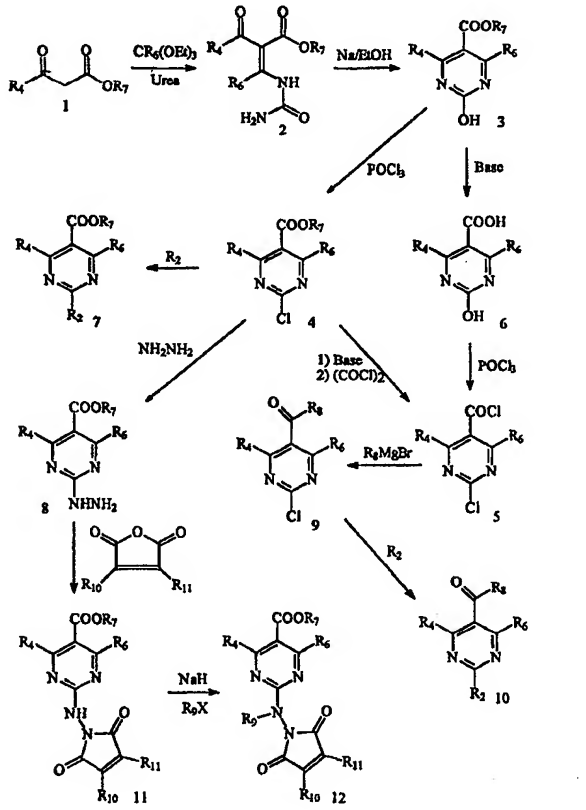
(54) Title: PYRIMIDINE CARBOXYLATES AND RELATED COMPOUNDS AND METHODS FOR TREATING INFLAMMATORY CONDITIONS

(57) Abstract

Compounds having utility as anti-inflammatory agents in general and, more specifically, for the prevention and/or treatment of immuno-inflammatory and autoimmune diseases are disclosed. The compounds are pyrimidine-containing compounds and, in one embodiment, are esters of the same. Methods are also disclosed for preventing and/or treating inflammatory conditions by administering to an animal in need thereof an effective amount of a compound of this invention, preferably in the form of a pharmaceutical composition.



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Description

PYRIMIDINE CARBOXYLATES AND RELATED COMPOUNDS AND METHODS FOR TREATING INFLAMMATORY CONDITIONS

Technical Field

The present invention relates generally to compounds that block intracellular signal transduction and activation of transcription factors, and to methods for preventing or treating immunoinflammatory and autoimmune diseases.

Background of the Invention

Signals necessary for cell growth, differentiation, response to bioregulatory molecules, infectious agents and physiological stress involve changes in the rates of gene expression. The ability to respond appropriately to such signaling events challenge the survival of the cell and ultimately the organism. Perturbations in the normal regulation of these specific genetic responses can result in pathogenic events which lead to acute and chronic disease.

In certain autoimmune diseases or chronic inflammatory states, continuous activation of T-cells eventually leads to a self-perpetuating destruction of normal tissues or organs. This is caused by the induction of adhesion molecules, chemotaxis of leukocytes, activation of leukocytes and the production of mediators of inflammation. All of these events are regulated at the level of transcription for the production of new proteins, including cytokines. The production of cytokines, as well as a number of other cellular regulators, is controlled by a family of proteins known as transcription factors (TFs). These transcription factors, when activated, bind to specific regions on the DNA and act as molecular switches or messengers to induce or upregulate gene expression. The activation of these TFs is caused by a variety of external signals including physiological stress, infectious agents and other bioregulatory molecules. Once the plasma membrane receptors are activated, a cascade of protein kinases and second messengers are induced which, in turn, result in the production of

RNA transcripts. The end result is the production of proinflammatory proteins via translation and processing of the RNA transcripts.

This activation system can, at times, be very robust. For example, a specific set of external signals could result in a single transcription factor to induce many proteins responsible for a given disease. Therefore, regulating this process by disrupting the production of activated TF(s) has the potential to attenuate the production of the associated pathological proteins, thereby halting or reversing the course of the disease.

Two transcription factors, NFκB and AP-1, have been shown to regulate the production of many proinflammatory cytokines and related proteins that are elevated in immunoinflammatory diseases. These TFs regulate interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor-α (TNFα), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels in a variety of cell types. For example, NFκB and other related complexes are involved in the rapid induction of genes whose products function in protective and proliferative responses upon exposure of cells to external stimuli. Similarly, AP-1 has a significant role in the regulation of interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α) transcription during T-cell activation. In addition, TNF-α and IL-1 are strong activators of collagenase, gelatinase and stromelysin gene expression, which require a single AP-1 binding site in the promoter region of these genes. Therefore, an inhibitor of NFκB and/or AP-1 activation would coordinately repress the activities of a series of proteinases. In addition, cell adhesion molecules are also controlled by these TFs. All of these proteins have been shown to play a role in diseases, including osteoarthritis, transplant rejection, ischemia, reperfusion injury, trauma, certain cancers and viral disorders, and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus and juvenile diabetes. In summary, the role of these TFs is to act as a transducer for certain stimuli that lead to immune, inflammatory, and acute phase responses.

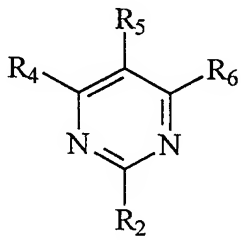
Since many diseases are caused by the inappropriate production of proteins, conventional therapeutic approaches have focused on inhibiting function or

activity of individual effector proteins. These treatments have not always proved to be effective and, at times, are associated with many undesirable side effects. Therefore, there is a need for new therapies for the prevention and/or treatment of immunoinflammatory and autoimmune diseases. More specifically, there is a need for compounds that prevent, preferably by inhibiting transcription at an early stage, the production of proteins associated with immunoinflammatory and autoimmune diseases. Furthermore, these compounds should inhibit the kinase(s) that regulate the activation of TFs such as NFκB and AP-1. The present invention fulfills these needs and provides further related advantages.

Summary of the Invention

In brief, this invention is directed to compounds that block the activation of transcription factors (TFs), particularly NFκB and AP-1, and are believed to function through inhibition of a family of specific kinases. This results in a decrease in a number of proinflammatory proteins, including IL-1, IL-2, IL-8 and/or TNFα, which are responsible for tissue and organ damage associated with diseases such as rheumatoid arthritis, osteoarthritis, related autoimmune disorders and tissue rejection. Accordingly, compounds of the present invention are useful in, for example, the prevention of organ and tissue rejection associated with transplantation. Furthermore, the compounds of this invention also have utility in the prevention and/or treatment of immunoinflammatory and autoimmune diseases, as well as having general activity as anti-inflammatory agents.

In one embodiment of this invention, compounds are disclosed having the following general structure (I):



(I)

wherein R_2, R_4, R_5 and R_6 are as defined in the following detailed description.

In another embodiment, a pharmaceutical composition is disclosed containing one or more compounds of this invention in combination with a pharmaceutically or prophylactically acceptable carrier or diluent.

In a further embodiment, methods are disclosed for preventing and/or treating inflammatory conditions by administering to a warm-blooded animal in need thereof an effective amount of a compound of this invention. Such inflammatory conditions include both immunoinflammatory conditions and autoimmune diseases. In the practice of the disclosed methods, the compounds are preferably administered to the warm-blooded animal in the form or a pharmaceutical composition.

These and other aspects of this invention will become evident upon reference to the attached figures and the following detailed description.

Brief Description of the Drawings

Figures 1 and 2 illustrate reaction schemes for the synthesis of representative compounds of this invention.

Figure 3 illustrates the ability of a representative compound of this invention to inhibit the activation of NFκB and AP-1.

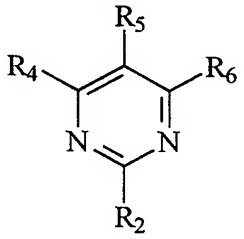
Figure 4 illustrates the ability of a representative compound of this invention to inhibit IL-2 and IL-8.

Detailed Description of the Invention

As mentioned above, the compounds of this invention block activation of transcription factors (TFs), and thus have utility as anti-inflammatory agents in general, and in the prevention and/or treatment of a variety of conditions, including (but not limited to) immunoinflammatory and autoimmune diseases. The compounds are believed to function by inhibiting, at an early stage, transcription of deleterious proteins associated with such conditions or diseases. It is believed that this is achieved by inhibiting the kinase(s) that regulate the activation of TFs, such as NFκB and/or AP-1. By disrupting the production of these activated TFs, synthesis of pathological proteins, including proinflammatory cytokines, associated with a series of immunoinflammatory

and autoimmune diseases are effectively blocked at a transcriptional level. Accordingly, the compounds of this invention have activity in both the prevention and treatment of immunoinflammatory diseases such as rheumatoid arthritis, osteoarthritis and transplant rejection (tissue and organ), as well as autoimmune diseases such as multiple sclerosis.

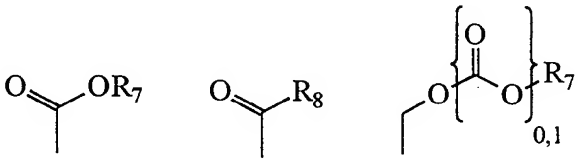
The compounds of this invention are generally represented by the following structure (I):



(I)

wherein R_2, R_4, R_5 and R_6 are as defined below.

In structure (I) above, R_5 is selected from the following chemical moieties (i), (ii) and (iii):



(i) (ii) (iii)

wherein

R_7 is selected from hydrogen and an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl; and

R_8 is an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl. In a preferred embodiment, R_7 is a C_{1-8} alkyl, and in a more preferred embodiment is selected from methyl and ethyl. Further, in a preferred embodiment, R_8 is selected from methyl and phenyl.

The compounds of this invention further include pharmaceutically and prophylactically acceptable salts of compounds of structure (I). Compounds of structure (I) may contain proton donating groups (*e.g.*, a carboxylic acid group) and/or proton accepting groups (*e.g.*, a group with a nitrogen atom having a free lone pair of electrons, such as an amine group), and the salts of compounds of structure (I) may be formed and utilized in the practice of the invention. Thus, compounds of the invention may be in the form of a base addition salt (*i.e.*, a salt of a proton donating group) or in the form of an acid addition salt (*i.e.*, a salt of a proton accepting group), as well as the free acid or free base forms thereof.

Acid addition salts of a free base amino compound of the invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include acetic, ascorbic, benzenesulfonic, benzoic, fumaric, maleic, methanesulfonic, and succinic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric and nitric acids. Base addition salts of a free acid carboxylic acid compound of the invention may also be prepared by methods well known in the art, and may be formed from organic and inorganic bases. Thus, the compounds of this invention also include those salts derived from inorganic bases such as the hydroxide or other salt of sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like, and organic bases such as substituted ammonium salts.

As used herein, the above terms have the following meaning:

A "C_{1-8}alkyl" is a straight chain or branched, cyclic or non-cyclic, saturated or unsaturated carbon chain containing from 1 to 8 carbon atoms. In one embodiment, the C_{1-8}alkyl is a fully saturated, straight chain alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl. In another embodiment, the C_{1-8}alkyl is a fully saturated cyclic alkyl selected from (but not limited to) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylenecyclopropyl and methylenecyclohexyl. In still a further embodiment, the C_{1-8}alkyl is a fully saturated, branched alkyl selected from (but not limited to) isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl and isohexyl. In yet a

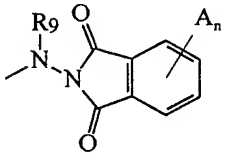
further embodiment, the C_{1-8}alkyl is an unsaturated straight chain alkyl selected from (but not limited to) ethylenyl, propylenyl, 1-butenyl, 1-pentenyl and 1-hexenyl.

A "C_{6-12}aryl" is an aromatic moiety containing from 6 to 12 carbon atoms. In one embodiment, the C_{6-12}aryl is selected from (but not limited to) phenyl, tetralinyl, and napthalenyl. In a preferred embodiment, the C_{6-12}aryl is phenyl.

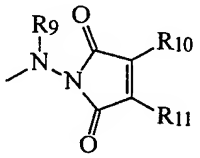
A "C_{7-12}aralkyl" is an arene containing from 7 to 12 carbon atoms, and has both aliphatic and aromatic units. In one embodiment, the C_{7-12}aralkyl is selected from (but not limited to) benzyl, ethylbenzyl, propylbenzyl and isobutylbenzyl.

A "substituted" C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl is a C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl having one or more hydrogens replaced with a substituent selected from halogen (including -F, -Cl, -Br and -I), -OH, -R, -OR, -COOH, -COOR, -COR, $-CONH_2$, $-NH_2$, -NHR, -NRR, $-NO_2$, -SH, -SR, -SOOR, $-SO_3R$ and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl as defined above. In one embodiment, the substituted C_{1-8}alkyl is a C_{1-8}haloalkyl including (but not limited to) $-CF_3$ and $-C_2F_5$.

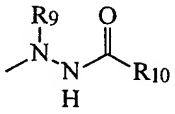
In one embodiment of structure (I) above, R_2 is R_{2a} and R_4 is R_{4a}. In this embodiment, R_{4a} is selected from hydrogen, halogen and an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl; and R_{2a} is selected from the following chemical moieties (iv) through (vii):



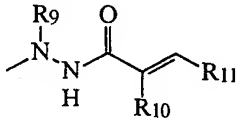
(iv)



(v)



(vi)



(vii)

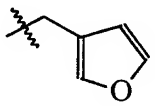
wherein R_9 is selected from hydrogen, -C(=O)-D-R_7 and an unsubstituted C_{1-8}alkyl or C_{7-12}aralkyl; and R_{10} and R_{11} are the same or different and independently selected from hydrogen and an unsubstituted or substituted C_{1-8}alkyl or C_{6-12}aryl; n is an integer from 0 to 4 and represents the number of substituents on the benzene ring of chemical moiety (iv); D represents a direct bond, -O- or -NH-; and each occurrence of A is independently

selected from a substituent as identified above. In a preferred embodiment, D is a direct bond; R_9 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$ and $-CH_2C_6H_5$; R_{10} and R_{11} are the same or different and independently selected from hydrogen, $-CH_3$, $-CF_3$, $-(CH_2)_{1-5}CH_3$, $-C_6H_5$, $-CH_2C_6H_5$, and a substituted phenyl or benzyl moiety; and n is 0.

In another embodiment of structure (I) above, R_2 is R_{2b} and R_4 is R_{4b}. In this embodiment, R_{2b} is selected from hydrogen, halogen and an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl; and R_{4b} is selected from chemical moieties (iv) through (vii) identified above.

As used herein, a "C_{3-12}heterocycle" is a moiety that contains a ring made up of more than one kind of atom, and which contains 3 to 12 carbon atoms. In one embodiment, the C_{3-12}heterocycle is selected from (but not limited to) pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, and thianaphthyl.

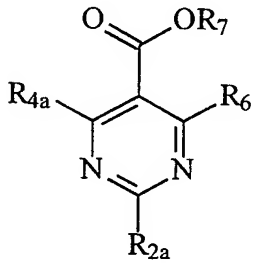
A "C_{4-16}heterocyclealkyl" is a moiety that contains a C_{3-12}heterocycle linked to a C_{1-8}alkyl, and which contains 4 to 16 carbon atoms. In one embodiment, the C_{4-16}heterocyclealkyl is a methylene furan having the following structure:



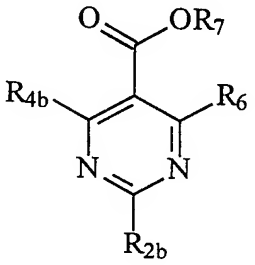
A "substituted" C_{3-12}heterocycle or C_{4-16}heterocyclealkyl is a C_{3-12}heterocycle or C_{4-16}heterocyclealkyl having one or more hydrogens replaced with a substituent selected from halogen (including -F, -Cl, -Br and -I), -OH, -R, -OR, -COOH, -COOR, -COR, $-CONH_2$, $-NH_2$, -NHR, -NRR, $-NO_2$, -SH, -SR, -SOOR, $-SO_3R$ and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl as defined above.

In structure (I) above, R_6 is selected from hydrogen, $-CH_3$, $-CH_2C_6H_5$, -F and $-CF_3$.

In one embodiment, the compounds of this invention have structure (I) above wherein R_5 is the chemical moiety (i). In this embodiment, the compounds disclosed herein have the following structures (II) and (III):



(II)



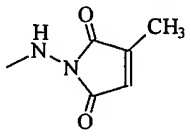
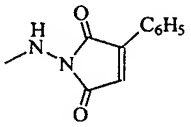
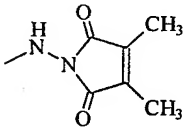
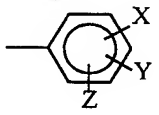
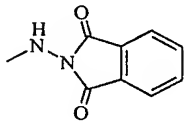
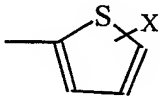
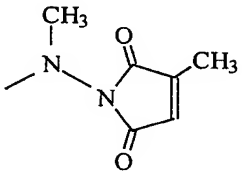
(III)

wherein R_{2a}, R_{2b}, R_{4a}, R_{4b}, R_6 and R_7 are as defined above.

In a preferred embodiment, the compounds of this invention have structure (II) above, wherein R_{2a}, R_{4a}, R_6 and R_7 are selected from the moieties identified in Table 1 below.

Table 1

Compounds of Structure (II)

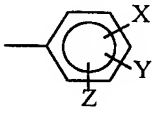
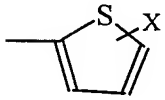
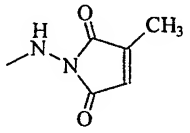
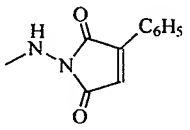
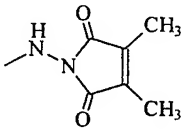
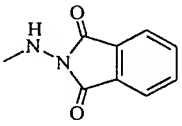
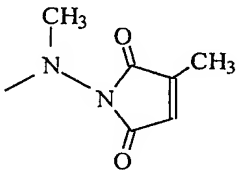
R_{2a}	R_{4a}	R_6	R_7
	-Cl $-CF_3$ $-CH_3$	-H $-CF_3$ $-CH_3$	$-CH_3$ $-CH_2CH_3$ -H
	-phenyl $-(CH_2)_{1-2}CH_3$ $-C_2F_3$		
			
			
			

wherein X, Y and Z are the same or different, and independently selected from hydrogen, -OH, -R, -OR, -COOH, -COOR, -COR $-CONH_2$, $-NH_2$, -NHR, -NRR, $-NO_2$, -SH, -SR, -SOOR, $-SO_3R$ and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl.

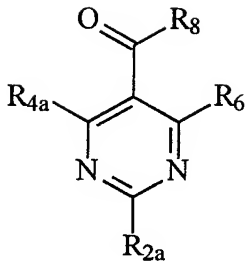
In a further preferred embodiment, the compounds of this invention have structure (III) above, wherein R_{2b}, R_{4b}, R_6 and R_7 are selected from the moieties identified in Table 2 below.

Table 2

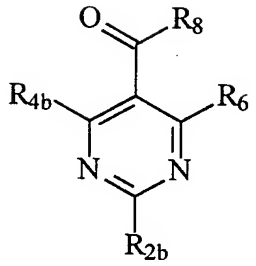
Compounds of Structure (III)

R_{2b}	R_{4b}	R_6	R_7
-Cl $-CF_3$ $-CH_3$ -phenyl $-(CH_2)_{1-2}CH_3$ $-C_2F_3$  	    	-H $-CF_3$ $-CH_3$	$-CH_3$ $-CH_2CH_3$ -H
wherein X, Y and Z are the same or different, and independently selected from hydrogen, -OH, -R, -OR, -COOH, -COOR, -COR $-CONH_2$, $-NH_2$, -NHR, -NRR, $-NO_2$, -SH, -SR, -SOOR, $-SO_3R$ and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl.			

In another embodiment, the compounds of this invention have structure (I) above wherein R_5 is the chemical moiety (ii). In this embodiment, the compounds disclosed herein have the following structures (IV) and (V):



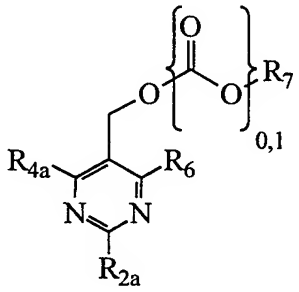
(IV)



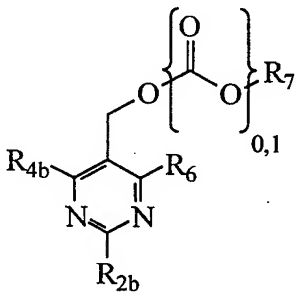
(V)

wherein R_{2a}, R_{2b}, R_{4a}, R_{4b}, R_6 and R_8 are as defined above.

In another embodiment, the compounds of this invention have structure (I) above wherein R_5 is the chemical moiety (iii). In this embodiment, the compounds disclosed herein have the following structures (VI) and (VII):



(VI)



(VII)

wherein R_{2a}, R_{2b}, R_{4a}, R_{4b}, R_6 and R_7 are as defined above.

In one embodiment, the compounds of this invention have structure (II) or (III) above and include (but are not limited to) the following: ethyl 2-(N-(1'-aminocitraconamido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminophthalimido))-4-trifluoromethylpyrimidine-5-carboxylate; 5-acetyl-2-(N-(1'-aminocitraconamido))-4-trifluoromethylpyrimidine; ethyl 2-(N-(1'-amino-3'-phenylmaleimido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-amino-3',4'-dimethylmaleimido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 4-(N-(1'-amino-3'-phenylmaleimido))-2-trifluoromethylpyrimidine-5-carboxylate; ethyl 4-

(N-(1'-amino-3',4'-dimethylmaleimido))-2-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-methylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-pentafluoroethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-phenylpyrimidine-5-carboxylate; methyl 2-(N-(1'-aminocitraconamido))-4-(3'-pyridyl)pyrimidine-5-carboxylate; diethyl 2-(N-(1'-aminocitraconamido))pyrimidine-4,5-dicarboxylate; ethyl 2-[N-(1'-amino-3'-methylsuccinimido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; methyl 2-[N-(1'-amino-3'-methylsuccinimido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-amino-4'-methylphthalimido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-amino-3,4-dichlorophthalimido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4-ethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-methyl]-4-ethyl-pyrimidine-5-carboxylate; ethyl 2-[N-acetyl-N-(1'-aminocitraconamido)]-4-propyl-pyrimidine-5-carboxylate; ethyl 2-[N-acetyl-N-(1'-aminocitraconamido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; methyl 2-[N-(1'-aminocitraconamido)]-4-pentafluoroethylpyrimidine-5-carboxylate; methyl 2-[N-(methyl)-N-(1'-amino-3'-methylmaleimido)]-4-pentafluoroethylpyrimidine-5-carboxylate; t-butyl-2-[N-(1'-aminocitraconamido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; methyl-2-[N-(1'-aminocitraconamido)]-4-trifluoromethyl-pyrimidine-5-carboxylate; methyl-2-[N-(1'-aminocitraconamido)-N-methyl]-4-trifluoromethyl-pyrimidine-5-carboxylate; methyl 2-[N-(1'-aminocitraconamido)]-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-benzyl]-4-trifluoromethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-methyl]-4-(2'-thienyl)pyrimidine-5-carboxylate; 2-[N-(1'-aminocitraconamido)]-4-trifluoromethyl-pyrimidine-5-carboxylic acid; ethyl 2-[N-(1'-aminocitraconamido)]-4-(3'-thienyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-methyl]-4-(3'thienyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4-(5'-methyl-2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4-(2'-furanyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-methyl]-4-(5'-methyl-2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-[(1'-amino-3'-methylmaleimido)]-

4-(2'-thianaphthyl)pyrimidine-5-carboxylate; methyl-2-[N-(1'-aminocitraconamido)-N-ethyl]-4-trifluoromethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-butanoyl]-4-trifluoromethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-(N-methylcarboxamidyl)-]-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-(1-oxo-2-phenylethyl)]-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4-methoxymethylpyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-(ethoxycarbonyl)]-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-benzoyl]-4-trifluoromethylpyrimidine-5-carboxylate; ethyl-2-[N-(1'-aminocitraconamido)-N-methyl]-4-pentafluoroethyl-pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4- (2'-thianaphthyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4-(2'-thiazolyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)-N-methyl]-4-(2'-thiazolyl)pyrimidine-5-carboxylate; ethyl 2-[N-(1'-aminocitraconamido)]-4-cyclopropylpyrimidine-5-carboxylate; and ethyl 2-[N-(1'-aminocitraconamido)-N-methyl]-4-cyclopropylpyrimidine-5-carboxylate.

In another embodiment, the compounds of this invention have structure (IV) or (V) above and include (but are not limited to) the following: 5-benzoyl-2-chloro-4-trifluoromethylpyrimidine; 5-acetyl-2-[N-(1'-aminocitraconamide)]-4-trifluoromethylpyrimidine; 5-benzoyl-2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine; 5-benzoyl-2-[N-(1'-aminocitraconamido)]-4-ethylpyrimidine; 5-benzoyl-2-[N-(1'-aminocitraconamido)-N-methyl]-4-ethylpyrimidine; and 5-butanoyl-2-[N-(1'-aminocitraconamido)-N-methyl]-4-ethylpyrimidine.

In yet another embodiment, the compounds of this invention have structures (VI) or (VII) above, and include (but are not limited to) the following: 5-methylol-2-[N-(1'-aminocitraconamido)]-4-ethylpyrimidine; 5-methylol-2-[N-(1'-aminocitraconamido)-N-methyl]-4-ethylpyrimidine; 5-methoxymethane-2-[N-(1'-aminocitraconamido)-N-methyl]-4-ethylpyrimidine; 5-methoxymethane-2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine; and 5-ethoxymethylcarbonate-2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine.

Preferred compounds of the invention are ethyl 2-(N-(1'-aminocitraconamido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminophthalimido))-4-trifluoromethylpyrimidine-5-carboxylate; 5-acetyl-2-(N-(1'-aminocitraconamido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-amino-3'-phenylmaleimido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-amino-3',4'-dimethylmaleimido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 4-(N-(1'-amino-3'-phenylmaleimido))-2-trifluoromethylpyrimidine-5-carboxylate; ethyl 4-(N-(1'-amino-3', 4'-dimethylmaleimido))-2-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-methylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-pentafluoroethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-phenylpyrimidine-5-carboxylate; methyl 2-(N-(1'-aminocitraconamido))-4-(3'-pyridyl)pyrimidine-5-carboxylate; diethyl 2-(N-(1'-aminocitraconamido))pyrimidine-4,5-dicarboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-ethylpyrimidine-5-carboxylate; methyl 2-(N-(1'-aminocitraconamido))-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-(5'-methyl-2'-thienyl)pyrimidine-5-carboxylate; ethyl 4-(N-(1'-aminocitraconamido))-2-phenylpyrimidine-5-carboxylate; and ethyl 4-(N-(1'-aminocitraconamido))-2-(2'-thienyl)pyrimidine-5-carboxylate.

The compounds of this invention may be made by one skilled in organic synthesis by known techniques, as well as by the synthetic routes disclosed herein. Referring to Figure 1, the compounds of this invention may be made from commercially available β-keto esters **1** by heating at elevated temperatures (75-110°C) with a mixture of urea and triethylorthoformate (or a substituted orthoformate) to provide ureido derivatives **2**. Treatment of these intermediates with sodium alkoxides, such as sodium ethoxide in an alcoholic solvent at 35-100°C, gives 2-hydroxypyrimidine esters **3** which, upon treatment with a chlorinating agent such as

phosphorous oxychloride at elevated temperatures (75-120°C), yields 2-chloropyrimidine esters **4**.

Compound **4** may be reacted with various nucleophiles in an aprotic solvent at ambient temperature to provide derivatives **7**. Compound **4** may also be converted to the carbonyl chloride **5** by treatment with base, such as hydroxide in water, followed by a chlorinating agent, such as oxalyl chloride in methylene chloride. Compound **5** can be treated with an organometallic, such as methyl magnesium bromide in a solvent such as THF or ether at -35°C to -65°C, to give ketone **9**. This ketone may be treated with various nucleophiles in an aprotic solvent and at ambient temperature to provide compound **10**.

Alternatively, compound **3** may be converted to the hydroxy carboxylic acid **6** by treatment with a strong base, such as sodium hydroxide, or strong acid, such as HCl, at elevated temperature (70-110°C). The hydroxy carboxylic acids may be converted to the chloro carbonyl chloride with thionyl chloride and/or phosphorous oxychloride.

Compound **4** can also be treated with hydrazine at ambient temperature in a solvent, such as THF, with pyridine as a catalyst to provide the intermediates of structure **8**. These hydrazino derivatives can be reacted with cyclic anhydrides, such as citraconic anhydride, in a solvent, such as chloroform, at elevated temperatures (35-65°C) to provide compounds of structure **11**. Subsequent treatment of **11** with a strong base, such as sodium hydride, in an aprotic solvent, such as THF, at ambient temperature followed by an alkyl iodide, such as methyl iodide, provides the alkylated derivatives of structure **12**.

Compounds of structures (VI) and (VII) may be prepared by reducing any of the compounds in Figure 1 so as to convert a carboxylate group to a methylol ($-CH_2OH$) group. Lithium aluminum hydride is a suitable reducing agent. In any event, the methylol group may, if desired, be converted to $-CH_2OR_7$ by standard alkylation chemistry (*e.g.*, using a strong base and a nucleophile).

Referring to Figure 2, an alternative synthetic procedure is disclosed. In this procedure, commercially available diethyl ethoxymethylenemalonate **13** is treated

with an amidine, such as trifluoromethylamidine, in a protic solvent, such as ethanol, in the presence of an alkoxide, such as NaOEt, at elevated temperatures (75-110°C) to give the hydroxy pyrimidine ester **14**. Chlorination with a chlorinating agent, such as $POCl_3$ or thionyl chloride, yields the chloroester derivative **15** which can be treated with various amines at ambient temperature in an aprotic solvent, such as THF, to provide the substituted pyrimidines **16**. Derivative **15** may also be treated with hydrazine in a solvent such as THF in the presence of pyridine to give the hydrazino intermediates **17**. Treatment of **17** with various cyclic anhydrides, such as citraconic anhydride, in a solvent, such as chloroform, at elevated temperatures (34-65°C) provide compounds of structure **18**. Alkylation of these compounds with a hydride, such as sodium hydride, followed by an alkyl halide in an aprotic solvent, such as THF, gives the alkylated derivatives of structure **19**.

Again, compounds of structures (VI) and (VII) may be prepared from the corresponding carboxylate compounds as discussed above in connection with Figure 1. Compounds of the invention wherein R_9 is $-C(=O)R_7$ may be prepared from the corresponding compound wherein R_9 is hydrogen (as prepared according to either of Figure 1 or 2) using standard acylation chemistry. For example, a compound having R_9 equal to hydrogen may be treated with a strong base (*e.g.*, NaH), followed by an acylating agent (*e.g.*, $Cl-C(=O)R_7$).

Once synthesized, the compounds of this invention may be formulated for administration to a warm-blooded animal by a variety of techniques known to those skilled in the art. In one embodiment, the compound is in the form of a pharmaceutical composition for prophylactic or therapeutic use, and which contains at least one compound of this invention in combination with a pharmaceutically acceptable carrier or diluent. The compound is present in the composition in an amount which, upon administration to the animal, is effective in preventing or treating the condition of interest. Preferably, the composition includes a compound of this invention in an amount ranging from 0.01 mg to 250 mg per dosage, depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations,

dosages and modes of administration may be readily determined by one skilled in the art.

Suitable carriers or diluents are familiar to those skilled in the formulation field. For compositions formulated as liquid solutions, acceptable carrier or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions of this invention may also be formulated as pills, capsules, granules or tablets which contain, in addition to the compound of this invention, diluents, dispersing and surface active agents, binders and lubricants. One skilled in the art may further formulate the compounds of this invention in any appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1990 (incorporated herein by reference).

In another embodiment, the present invention provides methods for preventing or treating a variety of conditions. Such methods include administering a compound of this invention to a warm-blooded animal in need thereof in an amount sufficient to prevent or treat the condition. Such methods include systemic administration of a compound of this invention, preferably in the form of a composition as disclosed above. As used herein, systemic administration includes oral and parental methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets and capsules, as well as liquids, syrups, suspensions and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention may be prepared in aqueous injectable solutions which may contain, in addition to the compound of this invention, buffers, antioxidants, bacteriostats and other additives commonly employed in such solutions.

As mentioned above, compounds of the present invention can be used to prevent or treat a wide variety of disorders, diseases and/or illnesses. In particular, the compounds may be administered to a warm-blooded animal for prevention or treatment of rheumatoid arthritis, osteoarthritis, tissue and/or organ transplant rejection, sepsis,

ARDS, asthma, trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer, viral infection, and autoimmune diseases such as psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis and chronic hepatitis.

Compounds of this invention may be screened by known and accepted techniques for their ability to function as prophylactically and/or therapeutically active agents. For example, the compounds may be evaluated in *in vitro* and/or *in vivo* assays indicative of the compound's anti-inflammatory and immunosuppressive properties. To this end, such compounds may first be evaluated in a number of cell-based assays which determine the ability of a compound to prevent activation of NFκB and AP-1 (*see* Example 126). Next, the compound's ability to attenuate cytokine levels (such as IL-2 and IL-8), which are known to be elevated in certain disease states, may be determined (*see* Example 127). The compounds may then be evaluated in an appropriate animal model, including rodent models of inflammation and immunosuppression (*see* Example 128).

It should be recognized that, for example, in the case of immunosuppressive drugs and other agents which have utility for the treatment of rheumatoid arthritis (RA), numerous studies have been performed directed to the activity of such drugs. To this end, cyclosporin A has been used in clinical trials since the late 1970's as a second-line drug, and is recommended to be used only in patients with active RA. Thus, Experiment 128 may be performed utilizing cyclosporin A as a positive control. A recent review of such immunosuppressive drugs, including relevant assays for the same, is presented by R.P. Carlson in *Exp. Opin. Invest. Drugs* **4**(9):853-859, 1995 (incorporated herein by reference in its entirety, including cited references).

The following examples are presented for purpose of illustration, not limitation.

EXAMPLES

To summarize the examples that follow, Examples 1-124 disclose the synthesis of representative compounds of this invention, as well as intermediates thereto; Example 125 discloses the synthesis of representative compounds by

combinational chemistry techniques; Examples 126-127 disclose the ability of representative compounds of this invention to inhibit NFκB, AP-1 and cytokines; and Example 128 discloses assays for evaluating activity of representative compounds of this invention in both graft versus host disease and contact sensitivity models.

Example 1

2-CHLORO-5-[3',5'-BIS(TRIFLUOROMETHYL)PHENACYL]-4-TRIFLUOROMETHYLPYRIMIDINE

To magnesium turnings (0.026 g, 1.06 mmol) in Et_2O (15 mL) was added a solution of 3,5-bistrifluoromethyl iodobenzene (0.300 g; 0.882 mmol) in Et_2O (5 mL). The reaction was refluxed under an atmosphere of N_2 for 2 h and then cooled to 0°C. A solution of 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride (0.205 g, 0.838 mmol) in Et_2O (5 mL) was added dropwise via syringe. After stirring 1 hour at 0°C, water (15 mL) was added and the mixture extracted with Et_2O (2 X 20 mL). The organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed (SiO_2, hexanes/EtOAc 8:1) to give the title compound (0.078 g, 21% yield) as an oil; ^1H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.21 (s, 1H), 8.19 (s, 2H).

Example 2

5-BENZOYL-2-CHLORO-4-TRIFLUOROMETHYLPYRIMIDINE

The title compound was prepared as described in Example 1, but employing phenyl magnesium bromide (0.23 mL, 0.69 mmol) and the acid chloride (0.17 g, 0.69 mmol), resulting in a yield of 30%; ^1H NMR ($CDCl_3$) δ 8.81 (s, 1H), 7.4-7.8 (m, 5H).

Example 3

ETHYL UREIDOMETHYLENE ACETOACETATE

A mixture of ethyl acetoacetate (200 g, 1.54 mole), urea (105 g, 1.54 mole) and triethyl orthoformate (228 g, 1.54 mole) was heated at 140°C under N_2 for 22 h. The reaction mixture was cooled and filtered to provide the title compound in a 51% yield (156 g); m.p. 173-174°C.

Example 4

ETHYL UREIDOMETHYLENE BENZOYLACETATE

The title compound was prepared as described in Example 3, but employing ethyl benzoylacetate (30.0 g, 156 mmol), resulting in a yield of 21% (12g); m.p. 124-126°C.

Example 5

ETHYL 2-HYDROXY-4-METHYLPYRIMIDINE-5-CARBOXYLATE

A solution of ethyl ureidomethylene acetoacetate (50 g, 250 mmol) NaOEt (22.1 g, 325 mmol) in EtOH (500 mL) was stirred at room temperature under N_2 for 3 days. The resulting solid was filtered and dried to yield the title compound as a sodium salt in a yield of 88% (45 g); m.p. >220°C (dec.).

Example 6

ETHYL 2-HYDROXY-4-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 5, but employing ethyl ureidomethylene benzoyl acetate (12 g, 45 mmol), resulting in a yield of 15% (6 g); m.p. >260°C, (dec.).

Example 7

ETHYL 2-CHLORO-4-METHYLPYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 2-hydroxy-4-methylpyrimidine-5-carboxylate (5 g, 27.5 mmol) and $POCl_3$ (84 g, 550 mmol) was heated at reflux under N_2 for 1 h. The reaction was cooled and concentrated. The residue was partitioned between $CHCl_3$ and H_2O and the organic layer was dried (Na_2SO_4), filtered, and concentrated to yield the title compound in a yield of 27% (1.5 g); ^1H NMR ($CDCl_3$) δ 9.04 (s, 1H), 4.42 (q, 2H), 2.85 (s, 3H), 1.43 (t, 3H).

Example 8

ETHYL 2-CHLORO-4-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 7, but employing 2-hydroxy-4-phenylpyrimidine-5-carboxylate (6 g, 25 mmol) to give the title compound (5.5 g, 86%); m.p. 45-47°C.

Example 9

2-CHLORO-4-METHYLPYRIMIDINE-5-CARBOXYLIC ACID

A solution of ethyl 2-chloro-4-methylpyrimidine-5-carboxylate (1.0 g, 5 mmol), NaOH (0.24 g, 6 mmol) in H_2O (30 mL) was stirred at room temperature for 3 h. The solution was acidified with 6N HCl and the resulting solid was filtered and dried to give the title compound (0.67 g 78%), ^1H NMR (DMSO-d_6) δ 9.01 (s, 1H), 2.75 (s, 3H).

Example 10

2-CHLORO-4-PHENYLPYRIMIDINE-5-CARBOXYLIC ACID

The title compound was prepared as described in Example 9, but employing 2-chloro-4-phenylpyrimidine-5-carboxylate (4.5 g, 17 mmol), resulting in a yield of 87% (3.9 g); m.p. 105-110°C.

Example 11

2-CHLORO-4-METHYLPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of 2-chloro-4-methylpyrimidine-5-carboxylic acid (0.81 g, 4.70 mmol), oxalyl chloride (0.89 g, 7.05 mmol), DMF (2 drops) in CH_2Cl_2 (23 mL) was stirred at room temperature under N_2 for 4 h. The solution was concentrated and distilled to give the title compound (0.55 g, 61%); b.p. 90-100°C, 1.3 mm/Hg; ^{1}H NMR ($CDCl_3$) δ d 9.02 (s, 1H), 2.74 (s, 3H).

Example 12

2-CHLORO-4-PHENYLPYRIMIDINE-5-CARBONYL CHLORIDE

The compound was prepared as described above in Example 11, but employing 2-chloro-4-phenylpyrimidine-5-carboxylic acid (3.8 g, 14 mmol), resulting in a yield of 53%; m.p. 42°C.

Example 13

2-CHLOROPYRIMIDINE-5-CARBONYLCHLORIDE

The compound was prepared as described in the literature (*see* Arukwe, *J. Undheim, K. Acta Chemica Scand.* **B40**:764, 1986).

Example 14

ETHYL ETHOXYMETHYLENE-4,4,4-TRIFLUOROACETOACETATE

A solution of ethyl 4,4,4-trifluoroacetoacetate (46 g, 0.25 mol) triethyl orthoformate (74 g, 0.50 mol) and Ac_2O (77 g, 0.75 mol) was heated at 120-140°C for 7 h. The mixture was concentrated and distilled to give the title compound in a 98% yield (58.6 g); b.p. 80-90°C, 1.5 mm/Hg.

Example 15

ETHYL 2-TRIFLUOROMETHYL-4-HYDROXYPYRIMIDINE-5-CARBOXYLATE

A solution of diethyl ethoxymethylenemalonate (35.0 g, 162 mmol), trifluoroacetamidine (18 g, 162 mmol) and NaOEt (11.0 g, 162 mmol) in EtOH (200 mL) was heated at reflux for 6 h. The reaction mixture was concentrated and H_2O (48 mL) was added. The resulting solid was filtered, washed with Et_2O (300 mL) and H_2O (200 mL), and dried to give the title compound (21 g, 50% yield); m.p. >220°C (dec.); ^{1}H NMR (DMSO-d_6) δ 8.38, 4.16 (q, 2H), 1.25 (q, 3H).

Example 16

2-TRIFLURUROMETHYL-4-CHLOROPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of ethyl 2-trifluoromethyl-4-hydroxypyrimidine-5-carboxylate (5.00 g, 19.4 mmol) and NaOH (0.93 g, 23.3 mmol) in H_2O (20 mL) was stirred at 60°C for 15 h. The reaction was acidified (concentrated HCl) and concentrated until a solid began to form. The solid was filtered and dried to give 2-trifluoromethyl-4-hydroxypyrimidine-5-carboxylic acid (2.1 g, 53% yield); ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H).

A solution of 2-trifluoromethyl-4-hydroxypyrimidine-5-carboxylic acid (2.0 g, 10.4 mmol), $POCl_3$ (32 g, 212 mmol) and $SOCl_2$ (25 g, 212 mmol) was heated at reflux for 4 days. The reaction was concentrated and distilled (b.p. 90-95°C, 1.5 mm/Hg) to provide the title compound (2.1 g, 81% yield), ^{1}H NMR ($CDCl_3$) δ 9.45 (s, 1H).

Example 17

2-CHLORO-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBONYL CHLORIDE

A solution of ethyl 2-hydroxy-4-pentafluoroethylpyrimidine-5-carboxylate (4.0 g, 13 mmol) and NaOH (1.60 g, 39 mmol) in EtOH (20 mL) and H_2O (45 mL) was heated at reflux for 1 h. The solution was cooled and acidified (concentrated HCl). The resulting solid was filtered and dried to provide 2-hydroxy-4-

pentafluoroethylpyrimidine-5-carboxylic acid (3.3 g, 98% yield); ^{1}H NMR (DMSO-d_6) δ 9.90 (bs, 1H), 8.43 (s, 1H).

A solution of 2-hydroxy-4-pentafluoroethylpyrimidine-5-carboxylic acid (3.33 g, 12.9 mmol) in $SOCl_2$ (27.7 g, 233 mmol) was heated at reflux for 0.5 h. Then $POCl_3$ (35.6 g, 233 mmol) was added to the reaction mixture and heating continued for 36 h. The reaction mixture was then concentrated and distilled (b.p. 80-85°C, 1 mm/Hg) to give the title compound (1.2 g, 35% yield); ^{1}H NMR (DMSO-d_6) δ 9.18 (s, 1H).

Example 18

ETHYL 4-HYDRAZINO-2-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 4-chloro-2-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 0.79 mmol), hydrazine (0.18 g, 6.0 mmol) and THF was stirred for 1 h at room temperature. The solution was filtered and dried to give the title compound in a 96% yield; ^{1}H NMR ($CDCl_3$) δ 9.26 (bs, 1H), 8.90 (s, 1H), 4.40 (q, 2H), 4.24 (bs, 2H), 1.41 (t, 3H).

Example 19

ETHYL 2-HYDRAZINO-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing ethyl-2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 0.79 mmol), resulting in a yield of 91% (0.18 g); m.p. 89-90°C.

Example 20

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 2-hydrazino-4-trifluoromethylpyrimidine-5-carboxylate (0.18 g, 0.72 mmol) and citraconic anhydride (0.08 ml, 0.94 mmol) in $CHCl_3$ (10 ml) was refluxed for 0.5 h. The solution was cooled, concentrated and

chromatographed (SiO_2, hexanes/EtOAc) to give the title compound (0.10 g, 39% yield); ^1H NMR ($CDCl_3$) δ 9.94 (s, 1H), 7.72 (s, 1H), 6.53 (s, 1H), 4.41 (q, 2H), 2.19 (s, 3H), 1.36 (t, 3H).

Example 21

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing ethyl 4-hydrazino-2-trifluoromethylpyrimidine-5-carboxylate (0.19 g, 0.76 mmol), resulting in an 80% yield (0.21 g); m.p. 85-86°C.

Example 22

ETHYL 2-[N-(1'-AMINOPHTHALIMIDO)]-4-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 2-chloro-4-trifluoromethyl-5-pyrimidine ester (0.25 g, 1.0 mmol), N-aminophthalimide (0.17 g, 1.0 mmol) and pyridine (0.09 ml, 1.0 mmol) in THF was heated at 60°C for 5 h and then concentrated. The residue was chromatographed (SiO_2, hexanes/EtOAc, 1:1) to give the title compound (0.07 g, 17% yield); m.p. 46-48 °C.

Example 23

5-ACETYL-2-[N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE

To a solution of 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride (0.50 g, 2.0 mmol) in THF at -78°C under N_2 was added MeMgBr (0.75 ml, 2.3 mmol). The reaction was stirred 0.75 h, quenched with H_2O (1ml) and diluted with EtOAc (30 ml). The organic layer was washed with H_2O, brine and then dried over $MgSO_4$. The residue was chromatographed (SiO_2, hexanes/EtOAc, 2:1) to provide the 5-acetyl-2-chloro-4-trifluoromethylpyrimidine (0.20 g) in 43% yield. The title

compound was then prepared as described for ethyl 2-[N-(1'-aminocitraconamide)]-4-trifluoromethylpyrimidine-5-carboxylate of Example 20, resulting in a 29% yield (0.08 g); m.p. 61-62°C.

Example 24

ETHYL UREIDOMETHYLENE PROPIONOYLACETATE

The title compound was prepared as described in Example 3, but employing ethyl propionylacetate (5.15 g, 35.7 mmol), resulting in a yield 43% (3.29 g); m.p. 148-150°C.

Example 25

ETHYL UREIDOMETHYLENE BUTYRYLACETATE

The title compound was prepared as described in Example 3, but employing ethyl butyrylacetate (25 g, 158 mmol), resulting in a yield of 47% (17g); m.p. 145-147°C.

Example 26

ETHYL UREIDOMETHYLENE 2-THIENYLACETATE

The title compound was prepared as described in Example 3, but employing ethyl 2-thienoylacetate (7.22 g, 36.4 mmol), resulting in a yield of 41% (4.0 g); m.p. 149-150°C.

Example 27

ETHYL 2-HYDROXY-4-ETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 5, but employing ethyl ureidomethylene ethanoylacetate (2.5 g, 11.7 mmol), resulting in a yield of 52% (1.2 g); ^{1}H NMR (DMSO-d_6) δ 8.05 (d, 1H), 4.24 (q, 2H), 2.87 (m, 2H), 1.29 (t, 3H).

Example 28

ETHYL 2-HYDROXY 4-PROPYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 5, but employing ethyl ureidomethylene propionoylacetate (10.96 g, 48 mmol), resulting in a yield of 73% (7.3 g); ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1H), 4.35 (q, 2H), 3.0 (t, 2H), 1.75 (m, 2H), 1.37 (t, 3H), 1.0 (t, 3H).

Example 29

ETHYL 2-HYDROXY-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 5, but employing ethyl ureidomethylene 2-thiophenoylacetate (4.0 g, 14.9 mmol), resulting in a yield of 79% (2.9 g); m.p. 144-146°C.

Example 30

ETHYL 2-CHLORO-4-ETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 7, but employing ethyl 2-hydroxy-4-ethylpyrimidine-5-carboxylate (1.2 g, 6.1 mmol), resulting in a yield of 77% (1.0 g); GC/MS calcd for $C_9H_{11}N_2O_2Cl$ (M^+) 214, found 214.

Example 31

ETHYL 2-CHLORO-4-PROPYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 7, but employing ethyl 2-hydroxy-4-propylpyrimidine-5-carboxylate (1.05 g, 5 mmol), resulting in a yield of 79% (0.9 g); GC/MS calcd for $C_{10}H_{13}N_2O_2Cl$ (M^+) 228, found 228.

Example 32

ETHYL 2-CHLORO-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 7, but employing ethyl 2-hydroxy-4-(2'-thienyl)pyrimidine-5-carboxylate (1.0 g, 4.0 mmol), resulting in a yield of 19% (0.2g); GC/MS calcd for $C_{11}H_9N_2O_2SCl$ (M^+) 268, found 268.

Example 33

ETHYL 2-HYDRAZINO-4-ETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing ethyl 2-chloro-4-ethylpyrimidine-5-carboxylate (1 g, 4.7 mmol), resulting in a yield of 41% (0.4 g); GC/MS calcd for $C_9H_{14}N_4O_2$ (M^+) 210, found 210.

Example 34

ETHYL 2-HYDRAZINO-4-PROPYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing ethyl 2-chloro-4-propylpyrimidine-5-carboxylate (0.9 g, 3.9 mmol), resulting in a yield of 97% (0.85 g); GC/MS calcd for $C_{10}H_{16}N_4O_2$ (M^+) 224, found 224.

Example 35

ETHYL 2-HYDRAZINO-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing ethyl 2-chloro-4-(2'-thienyl)pyrimidine-5-carboxylate (0.2 g, 0.7 mmol), resulting in a yield of 92% (0.17 g); GC/MS calcd for $C_{11}H_{12}N_4O_2S$ (M^+) 264, found 264.

Example 36

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-ETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing ethyl 2-hydrazino-4-ethylpyrimidine-5-carboxylate (0.4 g, 1.9 mmol), resulting in a yield of 32% (0.13 g); ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 6.51 (s, 1H), 5.94 (s, 1H), 4.32 (m, 2H), 3.05 (q, 2H), 2.18 (s, 3H), 1.35 (m, 6H).

Example 37

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-PROPYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing ethyl 2-hydrazino-4-propylpyrimidine-5-carboxylate (0.77 g, 3.4 mmol), resulting in a yield of 73% (0.7 g); m.p. 103-105°C.

Example 38

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing ethyl 2-hydrazino-4-(2'-thienyl)pyrimidine-5-carboxylate (0.17 g, 0.64 mmol), resulting in a yield of 55% (0.127 g); m.p. 123-126°C.

Example 39

5-AMIDO-2-[N-(1'-AMINOCITRACONAMIDO)]-
4-TRIFLUOROMETHYLPYRIMIDINE

To a solution of 2-chloro-4-trifluoromethylpyrimidine-5-carbonyl chloride (0.50 g, 2.0 mmol) in THF at 0°C under N_2 was added 2M NH_3/MeOH (1.0 ml, 2.0 mmol). The reaction was stirred 5 minutes, diluted with EtOAc (10 ml), filtered and concentrated. Chromatography (SiO_2, hexanes/EtOAc, 4:1) provided the 5-amido-2-chloro-4-trifluoromethylpyrimidine (0.20 g) in 44% yield. The title compound was then prepared as described for ethyl 2-[N-(1'-aminocitraconamide)]-4-trifluoromethylpyrimidine-5-carboxylate, resulting in a 15% yield (0.04 g); ^{1}H NMR

($CDCl_3$) δ 8.69 (s, 1H), 8.30 (s, 1H), 6.52 (s, 1H), 6.51 (s, 1H), 6.28 (s, 1H), 2.19 (s, 3H).

Example 40

ETHYL 2-[N-(1'-AMINO-3'-PHENYLMALEIMIDO)]-4-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described for ethyl 2-[N-(1'-aminocitraconamide)]-4-trifluoromethylpyrimidine-5-carboxylate but employing 3-phenylmaleic anhydride (0.21 g, 1.2 mmol), resulting in a 74% yield (0.18 g); m.p. 52-53°C.

Example 41

ETHYL 2-[N-(1'-AMINO-3',4'-DIMETHYLMALEIMIDO)]-4-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described for ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate but employing 3,4-dimethylmaleic anhydride (0.08 g, 0.63 mmol), resulting in a 47% yield (0.10 g); m.p. 110-111°C.

Example 42

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

To a solution of ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethyl-pyrimidine-5-carboxylate (0.10 g, 0.29 mmol) in THF at 0°C under nitrogen was added NaH (0.01 g, 0.44 mmol). After 5 minutes, MeI (0.10 ml, 1.6 mmol) was added and the reaction was allowed to warm to room temperature. After stirring 0.5 h at room temperature, the reaction was diluted with EtOAc (15 mL), washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed (SiO_2, hexanes/EtOAc 8:1) to give the title compound (0.05 g, 60%

yield); ^{1}H NMR ($CDCl_3$) δ 9.05 (s, 1H), 6.48 (s, 1H), 4.37 (q, 2H), 3.61 (s, 3H), 2.17 (s, 3H), 1.35 (t, 3H).

Example 43

ETHYL 4-[N-(1'-AMINO-3'-PHENYLMALEIMIDO)]-2-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of ethyl 4-hydrazino-2-trifluoromethylpyrimidine-5-carboxylate (0.09 g, 0.36 mmol) and 3-phenylmaleic anhydride (0.13 g, 0.72 mmol) resulting in a 69% yield (0.10 g); m.p. 179-180°C.

Example 44

ETHYL 4-[N-(1'-AMINO-3', 4'-DIMETHYLMALEIMIDO)]-2-TRIFLUOROMETHYL-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of ethyl 4-hydrazino-2-trifluoromethylpyrimidine-5-carboxylate (0.09 g, 0.36 mmol) and 3,4-dimethylmaleic anhydride (0.09 g, 0.72 mmol) resulting in a 89% yield (0.12 g); m.p. 116-117°C.

Example 45

ETHYL 2-HYDRAZINO-4-METHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing a solution of ethyl 2-chloro-4-methylpyrimidine-5-carboxylate (0.08 g, 0.39 mmol) and hydrazine (0.06 g, 2.0 mmol) in THF (7.8 mL) resulting in a 93% yield (0.07 g); ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 6.64 (bs, 1H), 4.33 (q, 2H), 2.70 (s, 3H), 1.38 (t, 3H).

Example 46

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-METHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of ethyl 2-hydrazino-4-methylpyrimidine-5-carboxylate (0.07 g, 0.36 mmol) and citraconic anhydride (0.08 g, 0.72 mmol) resulting in a 52% yield (0.06 g); m.p. 49-50°C.

Example 47

ETHYL 2-HYDRAZINO-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing a solution of ethyl 2-chloro-4-pentafluoroethylpyrimidine-5-carboxylate (0.30 g, 0.99 mmol) and hydrazine (0.16 g, 5.0 mmol) in THF (20 mL) resulting in a 95% yield (0.28 g); ^{1}H NMR ($CDCl_3$) δ 8.86 (bs, 1H), 7.12 (bs, 1H), 4.37 (q, 2H), 1.72 (bs, 2H), 1.38 (t, 3H).

Example 48

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of ethyl 2-hydrazino-4-pentafluoroethylpyrimidine-5-carboxylate (0.28 g, 0.93 mmol) and citraconic anhydride (0.13 g, 1.1 mmol) resulting in a 68% yield (0.25 g); m.p. 73-74°C.

Example 49

ETHYL 2-HYDRAZINO-4-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing a solution of ethyl 2-chloro-4-phenylpyrimidine-5-carboxylate (0.09 g, 0.34

mmol) and hydrazine (0.06 g, 1.7 mmol) in THF resulting in a 91% yield (0.08 g); m.p. 74-75°C.

Example 50

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of ethyl 2-hydrazino-4-phenylpyrimidine-5-carboxylate (0.08 g, 0.31 mmol) and citraconic anhydride (0.04 g, 0.37 mmol) resulting in a 64% yield (0.07 g); m.p. 165-167°C.

Example 51

ETHYL 2-HYDRAZINO-4-BENZYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing a solution of ethyl 2-chloro-4-benzylpyrimidine-5-carboxylate (0.34 g, 1.2 mmol) and hydrazine (0.2 g, 6.1 mmol) in THF resulting in a 99% yield (0.33 g, oil); GC/MS, 272(M^+).

Example 52

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-BENZYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of ethyl 2-hydrazino-4-benzylpyrimidine-5-carboxylate (0.34 g, 1.2 mmol) and citraconic anhydride (0.22 g, 2.0 mmol) resulting in a 37% yield (0.15 g) of the title compound; m.p. 34-36°C.

Example 53

METHYL 2-HYDROXY-4-(3'-PYRIDYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 5, but employing a solution of methyl ureidomethylene nicotinoyl acetate (8.4 g, 34 mmol) Na

(1.0 g, 44 mmol) in EtOH (200 mL) resulting in a 52% yield (4.4 g); ^{1}H NMR (DMSO-d_6) δ 8.59 (s, 1H), 8.51 (m, 2H), 7.72 (m, 1H), 7.36 (m, 1H), 3.51 (s, 3H).

Example 54

METHYL 2-CHLORO-4-(3'-PYRIDYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 7, but employing a solution of methyl 2-hydroxy-4-(3'-pyridyl)pyrimidine-5-carboxylate (4.42 g, 18 mmol) and $POCl_3$ (53.6 g, 350 mmol) resulting in a 25% yield (1.1 g); ^{1}H NMR (DMSO-d_6) δ 9.11 (s, 1H), 8.77 (m, 2H), 8.03 (m, 1H), 7.45 (m, 1H), 3.85 (s, 3H).

Example 55

METHYL 2-HYDRAZINO-4-(3'-PYRIDYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 18, but employing a solution of methyl 2-chloro-4-(3'-pyridyl)pyrimidine-5-carboxylate (0.10 g, 0.42 mmol) and hydrazine (67 mg, 2.1 mmol) resulting in a 97% yield (0.10 g); ^{1}H NMR (DMSO-d_6) δ 9.09 (s, 1H), 8.76 (d, 1H), 8.69 (d, 1H), 8.35 (bs, 1H), 7.89 (d, 1H), 7.42 (m, 1H), 3.76 (s, 2H), 2.19(bs, 2H).

Example 56

METHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(3'-PYRIDYL)-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution of methyl 2-hydrazino-4-(3'-pyridyl)pyrimidine-5-carboxylate (0.1 g, 0.39 mmol) and citraconic anhydride (0.04 g, 0.39 mmol) resulting in a 42% yield (0.06 g); m.p. 93-94°C.

Example 57

ETHYL 2-HYDROXY-4-BENZYLPYRIMIDINE-5-CARBOXYLATE

A solution of benzyl acetoacetate (7.0 g, 34 mmol) and N,N-dimethylformamide dimethyl acetal (4.0 g, 34 mmol) was stirred at room temperature for 0.25 h. The solution was concentrated and treated with urea (2.2 g, 37 mmol) and Na (1.2 g, 51 mmol) in EtOH (100 mL). The mixture was heated at reflux for 18 h, concentrated, acidified and purified by chromatography (SiO_2) to yield the desired product (2.6 g, 30%); m.p. 57-61°C.

Example 58

ETHYL 2-CHLORO-4-BENZYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 7, but employing a solution of ethyl 2-hydroxy-4-benzylpyrimidine-5-carboxylate (1.1 g, 4.3 mmol) and $POCl_3$ (16 g, 107 mmol) resulting in a 37% yield (0.44 g); ^1H NMR (DMSO-d_6) δ 9.00 (s, 1H), 7.6-7.4 (m, 5H), 4.55 (s, 2H), 4.25 (q, 2H), 1.14 (t, 3H).

Example 59

DIETHYL UREIDOMETHYLENE OXALACETATE

A solution of diethyl oxalacetate (5.7 g, 30.4 mmol), triethyl orthoformate (8.8 g, 30 mmol) and urea (2.0 g, 30 mmol) was heated at reflux for 1.5 h. The product was filtered, washed with water and ether to give (3.5 g, 45%) of the title compound; ^1H NMR (DMSO-d_6) δ 11.29 and 10.81 (dd, 1H), 8.6-7.4 (m, 3H), 4.2 (m, 4H), 1.24 (m, 6H).

Example 60

METHYL UREIDOMETHYLENE NICOTINOYL ACETATE

The title compound was prepared as described in Example 3, but employing a solution of methyl nicotinoyl acetate (10 g, 56 mmol), triethyl

orthoformate (8.3 g, 56 mmol) and urea (3.4 g, 56 mmol) resulting in a 60% yield (8.4 g); ^{1}H NMR (DMSO-d_6) δ 10.85 and 10.36 (dd, 1H), 8.8-7.2 (m, 7H), 3.58 (d, 3H).

Example 61

DIETHYL 2-HYDROXYPYRIMIDINE-4,5-DICARBOXYLATE

A solution of diethyl ureidomethylene oxalacetate (18.3 g, 71 mmol) in xylene (95 mL) was heated at reflux for 18 h. The reaction was cooled and the resulting solid was filtered. The solid was recrystallized from EtOAc to give the desired compound (8.2 g, 48%); ^{1}H NMR (DMSO-d_6) δ 8.61 (s, 1H), 4.25 (m, 4H), 1.27 (m, 6H).

Example 62

DIETHYL 2-CHLOROPYRIMIDINE-4,5-DICARBOXYLATE

The title compound was prepared as described in Example 7, but employing a solution of diethyl 2-hydroxypyrimidine-4,5-dicarboxylate (1.0 g, 4.2 mmol) and $POCl_3$ (7.7 g, 50 mmol) resulting in a 30% yield (0.32 g); ^{1}H NMR ($CDCl_3$) δ 9.09 (d, 1H), 4.35 (m, 4H), 1.30 (m, 6H).

Example 63

DIETHYL 2-HYDRAZINOPYRIMIDINE-4,5-DICARBOXYLATE

The title compound was prepared as described in Example 18, but employing a solution of diethyl 2-chloroypyrimidine-4,5-dicarboxylate (0.21 g, 0.83 mmol) and hydrazine (0.13 g, 4.2 mmol) in THF (10 mL) resulting in 96% yield (0.20 g); ^{1}H NMR ($CDCl_3$) δ 8.93 (bs, 1H), 8.34 (bs, 1H), 4.40 (m, 4H), 4.18 (bs, 2H), 1.35 (m, 6H).

Example 64

DIETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-PYRIMIDINE-4,5-DICARBOXYLATE

The title compound was prepared as described in Example 20, but employing a solution diethyl 2-hydrazinopyrimidine-4,5-dicarboxylate (0.20 g, 0.79 mmol) and citraconic anhydride (0.11 g, 0.95 mmol) resulting in a 77% yield (0.21 g); ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.88 (bs, 1H), 6.53 (s, 1H), 4.35 (m, 4H), 2.16 (s, 3H), 1.33 (m, 6H).

Example 65

ETHYL 2-[N-(1'-AMINO-3'-METHYLSUCCINIMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

To a solution of ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.05 g, 0.15 mmol) in EtOH (20 ml) was added Pd/C (0.1 g). The reaction was stirred under an atmosphere of H_2 overnight. The mixture was filtered over celite and concentrated to give the title compound (0.047 g, 94% yield); ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.39 (s, 1H), 4.40 (q, 2H), 3.10 (m, 2H), 2.44 (m, 1H), 1.38 (m, 3H).

Example 66

METHYL 2-[N-(1'-AMINO-3'-METHYLSUCCINIMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 65, but employing methyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.02 g, 0.06 mmol), resulting in a yield of 94% (0.019 g); m.p. 66-68°C.

Example 67

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-[2'-(5"-CHLOROTHIENYL]PYRIMIDINE-5-CARBOXYLATE

A solution of 5-chlorothiophene-2-carboxylic acid (16.3 g, 0.1 mole) and carbonyl diimidazole (27.8 g, 0.17 mol) in THF (200 mL) was stirred 30 minutes. Bis(ethyl malonate)magnesium salt (14.4 g, 0.051 mol) was added and the mixture was refluxed for 7 hours, cooled to RT and concentrated. EtOAc (200 mL) and 6N HCl (50 mL) were added and the organic layer was separated, dried ($MgSO_4$), and concentrated. The ethyl 5-chloro-2-thiophenoylacetate (23 g, 0.1 mol) and N,N-dimethylformamide dimethyl acetal (12 g, 0.1 mol) were stirred for 1 hour and concentrated. To this was added, a solution of NaOEt previously prepared using sodium in EtOH [Na (2.3 g, 0.1 mol) dissolved in 500 mL EtOH] and S-methyl isothiouronium sulfate (13.9 g, 0.05 mol) that was allowed to stir for 30 minutes. The mixture was refluxed for 4 hours, cooled to RT, concentrated, dissolved in EtOAC (500 mL), washed with 4N HCl (2 x 50 mL), dried ($MgSO_4$) and the solvent replaced with CH_2Cl_2 (300 mL). The solution was cooled to 0°C, mCPBA (51 g, 0.3 mol) was slowly added, and the solution was allowed to reach RT. After stirring for 2 hours, the solution was quenched by slowly pouring into a cold satd. $NaHSO_3$ solution (100 mL). The organic layer was then washed with satd. $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated. From this, the title compound was prepared as described in Example 20, but employing the ethyl 2-hydrazino-4-[2'-(5'-chlorothiophene)]pyrimidine-5-carboxylate (3.0 g, 0.017 mol) {prepared according to the procedure of Example 19, but employing ethyl 2-mesyl-4-[2'-(5'-chlorothiophene)]pyrimidine-5-carboxylate described above}, resulting in a yield of 38% (1.3 g); m.p. 137-138°C.

Example 68

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-[2'-(5"-CHLOROTHIENYL]PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 67 from 4-[2'-(5'-chlorothiophene)-2-hydrazino-5-pyrimidine carboxylate (0.5 g, 1.7 mmol), but employing methyl hydrazine (0.35 g, 7.5 mmol) where hydrazine was used, resulting in a yield of 48% (0.32 g); GC/MS calcd for $C_{17}H_{15}N_4O_4SCl$ (M+) 406, found 406.

Example 69

ETHYL 2-[N-(1'-AMINO-4'-METHYLPHTHALIMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, employing ethyl 2-hydrazino-4-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 0.8 mmol) and 4-methylphthalic anhydride (0.26 g, 1.6 mmol) where citraconic anhydride was used, resulting in a yield of 29% (0.09 g); m.p. 50-51°C.

Example 70

ETHYL 2-[N-(1'-AMINO-4',5'-DICHLOROPHTHALIMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, employing ethyl 2-hydrazino-4-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 0.8 mmol) and 4,5-dichlorophthalic anhydride (0.35 g, 1.6 mmol) where citraconic anhydride was used, resulting in a yield of 61% (0.22 g); m.p. 142-144°C.

Example 71

ETHYL 2-[N-(1'-CITRACONAMIDO)]-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) treating 2-chloropyrimidine-5-carbonylchloride (Example 13, 110 mg, 0.62 mmol) with ethanol (200 mg, 4.4 mmol in 1 mL of ethyl acetate) to provide 60% of ethyl 2-chloropyrimidine-5-carboxylate, (b) reaction of ethyl 2-chloropyrimidine-5-carboxylate (70 mg, 0.37 mmol) with hydrazine (100 mg, 3 mmol) to afford 44% of ethyl 4-hydrazinopyrimidine-5-carboxylate as in Example 19, (c) reaction of ethyl 4-hydrazinopyrimidine-5-carboxylate (0.36 g, 2.0 mmol) with citraconic anhydride (0.34 g, 3.0 mmol) in analogy to Example 21 to afford 10% (0.05 g) of the title compound; m.p. 95-98°C

Example 72

5-BENZOYL-4-ETHYL-2-METHYLTHIOPYRIMIDINE

The title compound was prepared by (a) reaction of ethyl propionylacetate (19.4 g, 0.13 mol) and N,N-dimethylformamide dimethyl acetal (16.0 g, 0.13 mol) in analogy to Example 67, (b) reaction with NaOEt (0.18 mol) and S-methyl isothouronium sulfate (18.7 g, 0.067 mol) also described for Example 67, (c) hydrolysis of the ethyl 4-ethyl-2-methylthiopyrimidine-5-carboxylate (18.0 g, 0.08 mmol) with NaOH (12.7 g, 0.32 mol) in H_2O (200 mL) as described in Example 67, (d) reaction of the 4-ethyl-2-methylthiopyrimidine-5-carboxylic acid (0.50 g, 2.5 mmol) and oxalyl chloride (0.32 g, 2.5 mmol) as described in Example 11, and (e) reaction of the 4-ethyl-2-methylthiopyrimidine-5-carbonyl chloride (0.50 g, 2.3 mmol) and phenyl magnesium bromide as described for Example 23, resulting in a yield of 22% (0.14 g) from the 4-ethyl-2-methylthiopyrimidine-5-carboxylic acid;); ^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1H), 7.80 (d, 2H), 7.62 (t, 1H), 7.50 (t, 2H), 2.81 (q, 2H), 2.61 (s, 3H), 1.22 (t, 3H).

Example 73

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-ETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 42, but employing ethyl 2-[N-(1'-aminocitraconamido)]-4-ethylpyrimidine-5-carboxylate (0.05 g, 0.16 mmol), resulting in a yield of 76% (0.04g); ^{1}H NMR ($CDCl_3$) δ 8.80 (d, 1H), 6.46 (s, 1H), 4.30 (q, 2H), 3.58 (s, 3H), 3.18 (m, 2H), 2.16 (s, 3H), 1.33 (m, 6H).

Example 74

ETHYL 2-[N-ACETYL-N-(1'-AMINOCITRACONAMIDO)]-4-PROPYLPYRIMIDINE-5-CARBOXYLATE

Ethyl 2-[N-(1'-aminocitraconamido)]-4-propylpyrimidine-5-carboxylate (0.060 g, 0.19 mmole) and 1.5 mL of an acetic anhydride and pyridine (1:1 molar) solution were stirred overnight. Concentration and chromatography (SiO_2, hexanes/EtOAc, 3:2) provided the title compound (0.03 g, 44% yield); ^{1}H NMR ($CDCl_3$) δ 9.0 (s, 1H), 6.5 (s, 1H), 4.4 (q, 2H), 3.1 (t, 2H), 2.82 (s, 3H), 2.19 (s, 3H), 1.7 (m, 2H), 1.39 (t, 3H), 0.99 (t, 3H).

Example 75

ETHYL 2-[N-ACETYL-N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 74, but employing ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.14 g, 0.4 mmol), resulting in a yield of 67% (0.11 g); ^{1}H NMR ($CDCl_3$) δ 9.14 (s, 1H), 6.55 (s, 1H), 4.45 (q, 2H), 2.83 (s, 3H), 2.20 (s, 3H), 1.39 (t, 3H).

Example 76

METHYL 2-HYDRAZINO-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared according to the procedure of Example 47 but employing a solution of methyl 2-chloro-4-pentafluoroethylpyrimidine-5-carboxylate (0.55 g, 1.9 mmol; itself prepared by a reaction of methanol with 2-chloro-4-pentafluoroethylpyrimidine-5-carbonyl chloride (see Example 17)) and hydrazine (0.3 g, 9.4 mmol), resulting in a yield of 99% (0.54 g); ^{1}HNMR ($CDCl_3$) δ, 8.87 (s, 1H), 7.09 (s, 1H), 3.92 (s, 3H), 1.7 (s, 2H).

Example 77

METHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared according to the procedure of Example 20 but employing 2-hydrazino-4-pentafluoroethylpyrimidine-5-carboxylate (0.54 g, 1.9 mmol) and citraconic anhydride (0.25 g, 2.3 mmol), resulting in a yield of 98% (0.71 g); m.p. 94-95°C.

Example 78

METHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-N-METHYL]-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared according to the procedure of Example 73 but employing methyl 2-[N-(1'-aminocitraconamido)]-4-pentafluoroethylpyrimidine-5-carboxylate (0.05 g, 0.13 mmol), a base and methyl iodide (0.04 g, 0.26 mmol); ^{1}HNMR ($CDCl_3$) δ 9.02 (s, 1H), 8.79 (s, 1H), 6.49 (m, 1H), 3.92 (s, 3H), 3.59 (d, 3H), 2.16 (d, 3H).

Example 79

t-BUTYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from t-butyl 2-hydrazino-4-trifluoromethylpyrimidine-5-carboxylate (0.88 g, 3.2 mmol) (prepared as described for Example 19, but employing t-butyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate) as described in Example 20, resulting in a yield of 10% (0.12 g); ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 7. 50 (s, 1H), 6.53 (s, 1H), 2.20 (s, 3H), 1.55 (s, 9H).

Example 80

METHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from methyl 2-hydrazino-4-trifluoromethylpyrimidine-5-carboxylate (0.01 g, 0.42 mmol) (prepared as described for Example 19, but employing methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate) as described in Example 20, resulting in a yield of 69% (0.096 g); m.p. 118-120°C.

Example 81

METHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from methyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 6.1 mmol) as described in Example 42, resulting in a yield of 10% (0.02 g); ^{1}H NMR ($CDCl_3$) δ 9.05 (s, 1H), 6.49 (s, 1H), 3.91 (s, 3H), 3.62 (s, 3H), 2.18 (s, 3H).

Example 82

METHYL 2-HYDRAZINO-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 2-hydroxy-4-(2'-thienyl)pyrimidine-5-carboxylate (2.7 g, 10.8 mmol) and NaOH (1.3 g, 32.4 mmol) in H_2O (25 mL) was stirred overnight then acidified to pH<2 using concentrated HCl. The precipitate was collected, dried under vacuum, and $POCl_3$ (16.5 g, 108 mmol) was added. To this was added diethylaniline (1.6 g, 10.8 mmol), and the mixture was refluxed for 30 minutes. The solution was cooled, concentrated, poured over ice and extracted with ether (200 mL). The 2-chloro-4-(2'-thienyl)pyrimidine-5-carboxylic acid was then dissolved in CH_2Cl_2 (30 mL), treated with oxalyl chloride (5.4 g, 42.7 mmol) and DMF (2 drops), and allowed to stir overnight. The solution was then concentrated, dissolved in MeOH (10 mL) and concentrated after stirring 10 minutes. The title compound was prepared from the crude methyl 2-chloro-4-(2'-thienyl)pyrimidine-5-carboxylate as described in Example 19, resulting in a overall yield of 6% (0.16 g); GC/MS calcd for $C_{10}H_{10}N_4O_2S$ (M^+) 250, found 250.

Example 83

METHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from methyl 2-hydrazino-4-(2'-thienyl)pyrimidine-5-carboxylate (0.16 g, 0.64 mmol) according to the procedure of Example 20, resulting in a yield of 90% (0.20 g); m.p. 112-113°C.

Example 84

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-BENZYL)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-(hydrazino-1'-benzyl)-4-trifluoromethylpyrimidine-5-carboxylate (0.2 g, 0.78 mmol) (prepared according to the procedure of Example 19 but employing benzylhydrazine) as described in Example 20, resulting in a yield of 12% (0.05 g); ^{1}H NMR ($CDCl_3$) δ 9.08 (d, 1H), 7.3 (m, 5H), 6.39 (s, 1H), 5.21 (m, 2H), 4.37 (m, 2H), 2.09 (s, 3H), 1.37 (m, 3H).

Example 85

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-METHYL)]-4-(2'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-[N-(1'-aminocitraconamido)]-4-(2'-thienyl)pyrimidine-5-carboxylate (0.05 g, 0.14 mmol) according to the procedure of Example 42, resulting in a yield of 19% (0.01 g); ^{1}H NMR ($CDCl_3$) δ 8.83 (d, 1H), 7.78 (m, 1H), 7.41 (m, 1H), 7.10 (m, 1H), 6.47 (d, 1H), 4.34 (m, 2H), 3.61 (s, 3H), 2.20 (d, 3H), 1.33 (m, 3H).

Example 86

2-[N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLIC ACID

A solution of t-butyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 0.5 mmol) in concentrated formic acid (8 mL) was refluxed for one hour, cooled, diluted with H_2O (10 mL), extracted with EtOAc (2 x 20 mL), dried ($MgSO_4$) and concentrated. The solid was washed with CH_2Cl_2 (2 x 20 mL) and dried under vacuum to give the title compound in 60% yield (0.10 g); m.p. 107-109°C.

Example 87

5-BENZOYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-TRIFLUOROMETHYLPYRIMIDINE

The title compound was prepared from 5-benzoyl-2-hydrazino-4-trifluoromethylpyrimidine (0.15 g, 0.53 mmol) (prepared as described for Example 19, but employing 5-benzoyl-2-mesyl-4-trifluoromethylpyrimidine) as described in Example 20, resulting in a yield of 6% (0.015 g); ^{1}H NMR ($CDCl_3$) δ 8.5 (s,1H), 7.8 (m,2H), 7.65 (m,1H), 7.5 (m,2H), 6.5 (s,1H), 3.45 (s,1H), 2.2 (s,3H).

Example 88

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(3'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-hydrazino-4-(3'-thienyl)pyrimidine-5-carboxylate (0.22 g, 0.88 mmol) (prepared in the same manner as Example 35) as described in Example 20, resulting in a yield of 40% (0.11 g); m.p. 47-48°C.

Example 89

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-METHYL)]-4-(3'-THIENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-[N-(1'-aminocitraconamido)]-4-(3'-thienyl)pyrimidine-5-carboxylate (0.05 g, 0.14 mmol) as described in Example 42, resulting in a yield of 19% (0.01 g); 39-41°C.

Example 90

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-[2'-(5'-METHYLTHIENYL)]PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-hydrazino-4-[2'-(5'-methylthienyl)]pyrimidine-5-carboxylate (0.22 g, 0.88 mmol) (prepared in the same manner as Example 67) as described for Example 20, resulting in a yield of 40% (0.11 g); m.p. 138-139°C.

Example 91

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(2'-FURANYL) PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of ethyl 2'-furanoylacetate (10 g, 0.055 mol) with N,N-dimethylformamide dimethyl acetal (7.3 g, 0.055 mol) as described for Example 67, (b) subsequent reaction with a solution NaOEt (0.058 mol) and S-methyl isothouronium sulfate (7.7 g, 0.028 mol) also described for Example 67, (c) oxidation with mCPBA (9.8 g, 0.057 mol) also described for Example 67, (d) reaction with hydrazine (1.5 mL, 0.05 mol) as described for Example 19, and (e) reaction with citraconic anhydride (4 mL, 0.05 mol) as described for Example 20, resulting in an overall yield of 1% (0.18 g); m.p. 38-40°C.

Example 92

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-METHYL)]-4-[2'-(5'-METHYLTHIENYL)]PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-(1'-methylhydrazino)-4-[2'-(5'-methylthienyl)]pyrimidine-5-carboxylate (3.0 g, 10.0 mmol) (prepared in the same manner as Example 67 employing methyl hydrazine) as described in Example 20,

resulting in a yield of 40% (1.6 g); ^{1}H NMR ($CDCl_3$) δ 8.71 (d,1H), 7.7 (d,1H), 6.74 (d,1H), 6.5 (d,1H), 4.33 (q,2H), 3.6 (s,3H), 2.5 (d,3H), 2.2 (d,3H), 1.32 (t,3H).

Example 93

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(2'-THIANAPHTHYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of ethyl 2'-benzothienoylacetate (24.8 g, 0.1 mol) with N,N-dimethylformamide dimethyl acetal (7.3 g, 0.055 mol) as described for Example 67, (b) subsequent reaction with a solution of NaOEt (0.12 mol) and S-methyl isothouronium sulfate (13.9 g, 0.05 mol) also described for Example 67, (c) oxidation with mCPBA (8.5 g, 0.05 mol) also described for Example 67, (d) reaction with hydrazine (1.5 mL, 0.05 mol) as described for Example 19, and (e) reaction with citraconic anhydride (4 mL, 0.05 mol) as described for Example 20, resulting in an overall yield of 0.1% (0.05 g); m.p. 165-166°C.

Example 94

METHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-ETHYL)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from methyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.20 g, 0.61 mmol) as described for Example 42, but employing ethyliodide, resulting in a yield of 18% (0.04 g); ^{1}H NMR ($CDCl_3$) δ 9.01 (d, 1H), 6.48 (s, 1H), 4.05 (q, 2H), 3.87 (s, 3H), 2.14 (s, 3H), 1.27 (t, 3H).

Example 95

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-BUTANOYL)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.10 g, 0.29 mmol) as described for Example 74, but employing butyric anhydride, resulting in a yield of 23% (0.03 g); ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H), 6.54 (s, 1H), 4.42 (q, 2H), 3.17 (t, 2H), 2.18 (s, 3H), 1.77 (q, 2H), 1.36 (t, 3H), 1.01 (t, 3H).

Example 96

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-(N'-METHYLCARBOXAMIDYL)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

Ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimi-dine-5-carboxylate (0.05 g, 0.15 mmol) and methylisocyanate (0.3 mL) were heated to 60°C for 3 minutes and allowed to cool to RT. After 30 minutes, the residual isocyanate was removed under vacuum, and the solid was washed with hexanes to provide the title compound in a 70% yield (0.03 g); m.p. 132-134°C.

Example 97

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-(1"-OXO-2"-PHENYLETHYL]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

A solution of ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.04 g, 0.12 mmol), phenylacetylchloride (0.08 mL, 0.6 mmol) and pyridine (0.05 mL, 0.6 mmol), in CH_2Cl_2 (15 mL) was stirred 1.5 hours, washed with H_2O, dried ($MgSO_4$), concentrated and chromatographed (SiO_2, hexanes/EtOAc, 2:1) to give the title compound in 42% yield (0.021 g); ^{1}H NMR

($CDCl_3$) δ 9.11 (s, 1H), 7.27 (m, 5H), 6.53 (s, 1H), 4.46 (s, 2H), 4.42 (q, 2H), 2.17 (s, 3H), 1.37 (t, 3H).

Example 98

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-METHOXYMETHYL PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of ethyl methoxyketoacetate (10.5 g, 0.07 mol) with triethyl orthoformate (9.7 g, 0.07 mol) and urea (3.9 g, 0.07 mol) as described for Example 3, (b) reaction with NaOEt (0.02 mol) as described for Example 5, (c) reaction with $POCl_3$ (6.5 mL, 0.07 mol) as described for Example 7, (d) reaction with hydrazine (2 mL, 0.07 mol) as described for Example 19, and (e) reaction with citraconic anhydride (6 mL, 0.07 mol) as described for Example 20, resulting in an overall yield of 8% (1.8 g); ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1H), 8.2 (s, 1H), 6.5 (s, 1H), 4.87 (s, 2H), 4.35 (q, 2H), 3.47 (s, 3H), 2.18 (s, 3H), 1.35 (t, 3H).

Example 99

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-(ETHOXYCARBONYL)]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.06 g, 0.19 mmol) as described for Example 97, but employing ethyl chloroformate, resulting in a yield of 71% (0.055 g); ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H), 6.54 (s, 1H), 4.39 (m, 4H), 2.18 (s, 3H), 1.31 (m, 6H).

Example 100

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-BENZOYL]-4-TRIFLUOROMETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylate (0.09 g, 0.26 mmol) as described for Example 97, but employing benzoyl chloride, resulting in a yield of 69% (0.08 g); ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1H), 7.72 (d, 2H), 7.52 (dd, 1H), 7.41 (dd, 2H), 6.55 (s, 1H), 4.39 (q, 2H), 2.19 (s, 3H), 1.35 (t, 3H).

Example 101

5-BENZOYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-ETHYLPYRIMIDINE

The title compound was prepared by (a) reaction of 5-benzoyl-4-ethyl-2-methylthiopyrimidine (0.14 g, 0.54 mmol) and mCPBA (0.28 g, 1.6 mmol) as described for Example 67, (b) reaction with hydrazine (0.09 g, 2.7 mmol) as described for Example 19, and (c) reaction with citraconic anhydride as described for Example 20, resulting in a overall yield of 25% (0.046 g); m.p. 49-50°C.

Example 102

5-BENZOYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-ETHYLPYRIMIDINE

The title compound was prepared as described for Example 42, but employing 2-[N-(1'-aminocitraconamido)]-5-benzoyl-4-ethylpyrimidine (0.06 g, 0.18 mmol), resulting in a yield of 40% (0.025 g); ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 1H), 7.78 (d, 2H), 7.60 (dd, 1H), 7.44 (dd, 2H), 6.43 (s, 1H), 3.61 (s, 3H), 2.68 (m 2H), 2.19 (s, 3H), 1.2 (m 3H).

Example 103

ETHYL-2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-PENTAFLUOROETHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared according to the procedure of Example 78 but employing ethyl-2-[N-(1'-aminocitraconamide)]-4-pentafluoroethylpyrimidine-5-carboxylate (0.1 g, 0.3 mmol) and methyl iodide (0.07 g, 0.5 mmol) under basic conditions, resulting in a yield of 47% (0.05 g); ^{1}HNMR ($CDCl_3$) δ 9.01 (s, 1H), 8.80 (s, 1H), 6.49 (m, 1H), 4.39 (q, 2H), 3.62 (s, 3H), 2.18 (d, 3H), 1.36 (t, 3H).

Example 104

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(2"-THIANAPHTHYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared from ethyl 2-mesyl-4-(2'-thianaphthyl)pyrimidine-5-carboxylate (2.0 g, 5.5 mmol) as described in Example 93, but employing methyl hydrazine (0.9 mL, 16.5 mmol) where hydrazine was used, this followed by reaction with citraconic anhydride (1.5 mL, 16.5 mmol) also in anology to Example 93; resulting in a yield of 69% (1.6 g); ^{1}H NMR ($CDCl_3$) δ 8.8 (d, 1H), 8.15 (d, 1H), 7.8 (m, 2H), 7.3 (m, 2H), 6.6 (d, 1H), 4.37 (q, 2H), 3.65 (d, 3H), 2.17 (s, 3H), 1.34 (t, 3H).

Example 105

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-(2'-THIAZOLYL)PYRIMIDINE-5-CARBOXYLATE

2-Bromothiazole (8.25 g, 0.05 moles) in anhydrous ether (60 mL) is added dropwise to a solution of nBuLi (34 mL, 1.5M solution, 0.051 mmol) in anhydrous ether (60 mL) cooled to -78°C and stirred for 30 minutes. Carbon dioxide is bubbled into the solution and after saturation is achieved, the reaction mixture is poured

over dry-ice. H_2O (10 mL) is added and the mixture basified to pH=9 with NaOH (1 N). The aqueous layer is acidified with concentrated HCl to pH <3 then extracted into ether, dried ($MgSO_4$) and concentrated to provide the thiazole-2-carboxylic acid in 57% yield (3.2 g); ^{1}H NMR (MeOD) δ 8.00 (d, 1H); 7.94 (d, 1H). The title compound was then prepared by (a) reaction of thiazole-2-carboxylic acid (3.7 g, 29.0 mmol) and bis(ethyl malonate)magnesium salt (4.3 g, 15.0 mmol) as described in Example 67, (b) reaction of 2-thiazolylacetate (2.5 g, 12.8 mmol) and N,N-dimethylformamide dimethyl acetal (2.42 g, 12.8 mmol) as described for Example 67, (c) reaction with NaOEt (13.8 mol) and S-methyl isothouronium sulfate (1.78 g, 6.4 mol) also described for Example 67, (d) oxidation with mCPBA (6.1 g, 35.0 mmol) also described for Example 67, (e) reaction of ethyl 2-mesyl-4-(2'-thiazolyl)pyrimidine-5-carboxylate (1.08 g, 3.45 mmol) with hydrazine (0.33 mL, 10.3 mmol) as described for Example 19, and (f) reaction with citraconic anhydride (0.31 mL, 3.5 mmol) described for Example 20, resulting in an overall yield of 8% (0.10 g) from ethyl 2-mesyl-4-(2'-thiazolyl)pyrimidine-5-carboxylate; m.p 42-44°C.

Example 106

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-(2'-THIAZOLYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described in Example 20, but employing ethyl 2-(1'-methylhydrazino)-4-(2'-thiazolyl)pyrimidine-5-carboxylate (0.96 g, 3.4 mmol) (prepared according to the procedure of Example 19 but employing ethyl 2-mesyl-4-(2'-thiazolyl)pyrimidine-5-carboxylate and methyl hydrazine where hydrazine was used), resulting in a yield of 50% (0.64 g); ^{1}H NMR δ 8.69 (bs, 1H); 7.92 (d, 1H); 7.50 (d, 1H); 6.50 (d, 1H); 4.35 (q, 2H); 3.62 (s, 3H); 2.2 (s, 3H); 1.27 (t, 3H).

Example 107

5-BUTANOYL 2-[N-(1'-AMINOCITRACONAMIDO-N-METHYL)]-4-ETHYLPYRIMIDINE

The title compound was prepared as described for Example 101, but employing 5-butanoyl-4-ethyl-2-methylthiopyrimidine (1.16 g, 5.2 mmol) (prepared as described for Example 72) where 5-benzoyl-4-ethyl-2-methylthiopyrimidine was used, resulting in an overall yield of 15% (0.24 g); ^{1}H NMR δ 8.80 (d, 1H), 6.42 (d, 1H), 3.60 (s, 3H), 2.65 (m ,4H), 2.20 (s, 3H), 1.65 (m, 3H), 1.23 (m, 2H), 0.99 (m, 3H).

Example 108

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO)]-4-CYCLOPROPYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described for Example 67, but employing cyclopropanecarboxylic acid (5.5 g, 63.9 mmol) where 5-chlorothiophene-2-carboxylic acid was used, resulting in an overall yield of 0.8% (0.09 g); m.p. 76-78°C.

Example 109

ETHYL 2-[N-(1'-AMINOCITRACONAMIDO-N-METHYL)]-4-CYCLOPROPYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared as described for Example 108 from cyclopropanecarboxylic acid (5.5 g, 63.9 mmol), but employing methyl hydrazine where hydrazine was used, resulting in an overall yield of 0.3% (0.062 g); m.p. 53-55°C.

Example 110

4-ETHYL-5-(HYDROXYMETHYL)-2-METHYLTHIOPYRIMIDINE

To a solution of ethyl 4-ethyl-2-methylthiopyrimidine-5-carboxylic acid (2.0 g, 10.1 mmol) (prepared as described in steps a-c of Example 72) and N-methyl morpholine (1.16 mL, 10.6 mmol) in dimethyl glycol (50 mL) at 0°C was added isobutylchloroformate (1.38 mL, 10.6 mmol). The mixture was stirred 10 minutes, filtered, and cooled to 0°C. A solution of $NaBH_4$ (0.40 g, 10.6 mmol) in H_2O (10 mL) was added to the filtrate and the mixture was stirred for 10 minutes. H_2O (10 mL) was added and the mixture was extracted with EtOAc (100 mL),washed with brine (20 mL), and concentrated to provide the title compound in 56% yield (1.04 g); GC/MS calcd for $C_8H_{12}N_2OS$ (M^+) 184, found 184.

Example 111

2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-ETHYL-5-(HYDROXYMETHYL)PYRIMIDINE

A solution of 5-hydroxymethyl-4-ethyl-2-methylthiopyrimidine (0.50 g, 2.72 mmol), t-butyldimethylsilylchloride (0.49 g, 3.26 mmol), and imidazole (0.20 g, 2.99 mmol) in DMF (5 mL) was stirred overnight and concentrated to give of 5-t-butyldimethylsiloxymethyl-4-ethyl-2-methylthiopyrimidine in a 94% yield (0.76 g); GC/MS calcd for $C_{14}H_{26}N_2OSSi$ (M^+) 299, found 299. The title compound was then prepared by (a) oxidation of 5-t-butyldimethylsiloxymethyl-4-ethyl-2-methylthiopyrimidine (0.30 g, 1.0 mmol) with mCPBA (0.35 g, 2.0 mmol) as described for Example 67, (b) reaction with methyl hydrazine (0.16 mL, 3.0 mmol) followed by citraconic anhydride (0.11 g, 1.0 mmol) also described in Example 67; (c) reaction of 2-[N-(1'-aminocitraconamido)]-5-t-butyldimethylsiloxymethyl-4-ethylpyrimidine (0.08 g, 0.21 mmol) and concentrated HCl (0.5 mL) in EtOH (20 mL) for 1 hour, concentration and chromatography (Hexanes/EtOAc, 2:1) to provide the title compound in 76% yield (0.043 g) from 2-[N-(1'-aminocitraconamido)]-5-t-butyldimethylsiloxymethyl-4-ethylpyrimidine; m.p. 108-110°C.

Example 112

2-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-4-ETHYL-5-(METHOXYMETHYL)PYRIMIDINE

A solution of 4-ethyl-5-hydroxymethyl-2-methylthiopyrimidine (0.63 g, 3.42 mmol), Ag_2O (1.6 g, 6.9 mmol) and MeI (1.1 mL, 17.1 mmol) in CH_3CN (10 mL) was stirred overnight, filtered and concentrated to give 4-ethyl-5-methoxymethyl-2-methylthiopyrimidine in 98% yield (0.66 g); GC/MS calcd. for $C_9H_{14}N_2OS$ (M+) 198, found 198. The title compound was then prepared by (a) oxidation of 4-ethyl-5-methoxymethyl-2-methylthiopyrimidine (0.66 g, 3.35 mmol) with mCPBA (1.18 g, 6.85 mmol) as described for Example 67, and (b) reaction with methyl hydrazine (0.36 mL, 6.85 mmol) followed by citraconic anhydride (0.77 g, 6.85 mmol) also described in Example 67; resulting in a yield of 41% (0.40 g) from 4-ethyl-5-methoxymethyl-2-methylthiopyrimidine; ^{1}H NMR (CDCl3) δ 8.14 (s, 1H), 6.43 (s, 1H), 4.29 (s, 2H), 3.53 (s, 3H), 3.36 (s, 3H), 2.68 (m, 2H), 2.14 (s, 3H), 1.13 (m, 3H).

Example 113

2-[N-(1'-AMINOCITRACONAMIDO)]-5-(METHOXYMETHYL)-4-TRIFLUOROMETHYLPYRIMIDINE

The title compound was prepared as described for Example 112, but employing of 4-trifluoromethyl-5-hydroxymethyl-2-methylthiopyrimidine (0.50 g, 2.23 mmol) (prepared in analogy to Example 110) where 4-ethyl-5-hydroxymethyl-2-methylthiopyrimidine was used, and employing hydrazine (0.09 mL, 2.87 mmol) where methyl hydrazine was used, resulting in an overall yield of 35% (0.25 g); ^{1}H NMR (CDCl3) δ 8.63 (s, 1H), 8.20 (s, 1H), 6.48 (s, 1H), 4.46 (s, 2H), 3.75 (s, 3H), 2.12 (s, 3H).

Example 114

2-[N-(1'-AMINOCITRACONAMIDO)]-5-(ETHOXYMETHYLCARBONATE)-4-TRIFLUOROMETHYLPYRIMIDINE

To a solution of 2-[N-(1'-aminocitraconamido)]-4-trifluoromethylpyrimidine-5-carboxylic acid (0.10 g, 0.317 mmol) and N-methylmorpholine (0.035 mL, 0.317 mmol) in THF (10 mL) at 0°C was added ethylchloroformate (0.030 mL, 0.317 mmol). After stirring 5 minutes, $NaBH_4$ (0.040g, 1.05 mmol) was added, MeOH (7 mL) was added, and the mixture was stirred 10 minutes then concentrated. The oil was dissolved in EtOAc (30 mL) and washed with 1 N HCl (10 mL), 1 N $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), concentrated and chromatographed (SiO_2, hexanes/EtOAc, 2:1) to provide the title compound in 19% yield (0.022 g); ^1H NMR ($CDCl_3$) δ 9.03 (s, 1H), 6.53 (s, 1H), 4.88 (s, 2H), 4.36 (q, 2H), 2.19 (s, 3H), 1.32 (t, 3H).

Example 115

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of diethylethoxy-methylenemalonate (31 g, 144 mmol) with benzamidine (22 g, 144 mmol) under basic conditions to afford ethyl 2-phenyl-4-hydroxypyrimidine-5-carboxylate in 64% yield in analogy to Example 15, (b) reaction of ethyl 2-phenyl-4-hydroxypyrimidine-5-carboxylate (1.5 g, 6 mmol) and $POCl_3$ (9.4 g, 62 mmol) to afford 81% of ethyl 2-phenyl-4-chloropyrimidine-5-carboxylate in analogy to Example 7, (c) reaction of ethyl 2-phenyl-4-chloropyrimidine-5-carboxylate (12 g, 46 mmol) with hydrazine (4.4 g, 137 mmol) to afford 99% of ethyl 4-hydrazino-2-phenylpyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of ethyl 4-hydrazino-2-phenylpyrimidine-5-carboxylate (12 g, 46 mmol) with citraconic anhydride (10 g, 92 mmol) to afford 75% (12 g) of the title compound (m.p. 155-156°C) in analogy to Example 21.

Example 116

ETHYL-4-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-2-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared according to the procedure of Example 68 but employing ethyl 2-[N-(1'-aminocitraconamide)]-4-phenylpyrimidine-5-carboxylate (0.1 g, 0.3 mmol) and methyl iodide (0.09 g, 0.7 mmol) under basic conditions, resulting in a yield of 45% (0.05 g); m.p. 118-119°C.

Example 117

ETHYL 4-[N-ACETYL-N-(1'-AMINOCITRACONAMIDO)]-2-PHENYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared according to the procedure of Example 75 but employing ethyl 2-[N-(1'-aminocitraconamide)]-4-phenylpyrimidine-5-carboxylate (0.5 g, 1.3 mmol, prepared in Example 115) and acetic anhydride (5 mL) under basic conditions, resulting in a yield of 10% (0.05 g); ^{1}HNMR ($CDCl_3$) δ 9.15 (d, 1H), 8.19 (d, 2H), 7.47 (m, 3H), 6.70 (d, 1H), 4.42 (q, 2H), 2.28 (d, 6H), 1.43 (t, 3H).

Example 118

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-METHYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of diethylethoxymethylenemalonate (6 g, 28 mmol) with acetamidine hydrochloride (3 g, 31 mmol) to afford 67% of ethyl 2-methyl-4-hydroxypyrimidine-5-carboxylate in analogy to Example 15, (b) reaction of ethyl 2-methyl-4-hydroxypyrimidine-5-carboxylate (2.8 g, 15 mmol) with $POCl_3$ (46 g, 300 mmol) to afford 28% of ethyl 4-

chloro-2-methylpyrimidine-5-carboxylate, (c) reaction of ethyl 4-chloro-2-methylpyrimidine-5-carboxylate (0.25 g, 1.25 mmol) with hydrazine (0.2 g, 6.3 mmol) to afford 96% of 4-hydrazino-2-methylpyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of 4-hydrazino-2-methylpyrimidine-5-carboxylate (0.24 g, 1.2 mmol) with citraconic anhydride (0.16 g, 1.44 mmol) to afford 70% (0.24 g) of the title compound (m.p. 98-99°C) in analogy to Example 21.

Example 119

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-BENZYLPYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of diethyl ethoxymethylenemalonate (11 g, 52 mmol) with phenylacetamidine (8 g, 60 mmol) to afford 40% of ethyl 2-benzyl-4-hydroxypyrimidine-5-carboxylate in analogy to Example 15, (b) reaction of 2-benzyl-4-hydroxypyrimidine-5-carboxylate (3 g, 12 mmol) with $POCl_3$ (18 g, 116 mmol) to afford 45% of 2-benzyl-4-chloropyrimidine-5-carboxylate in analogy to Example 7, (c) reaction of 2-benzyl-4-chloropyrimidine-5-carboxylate (1.5 g, 5.5 mmol) with hydrazine (0.5 g, 16 mmol) to afford 75% of 2-benzyl-4-hydrazinopyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of ethyl 2-benzyl-4-hydrazinopyrimidine-5-carboxylate (1g, 3.5 mmol) with citraconic anhydride (1g, 11 mmol), in analogy to Example 21, to afford 70% (0.9 g) of the title compound; m.p. 117-118°C.

Example 120

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-(3'-NITROPHENYL)-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of diethyl ethoxymethylenemalonate (5 g, 24 mmol) with 3-nitrobenzamidine (5 g, 25 mmol) to afford 86% of ethyl 4-hydroxy-2-(3'-nitrophenyl)pyrimidine-5-carboxylate in analogy

to Example 15, (b) reaction of ethyl 4-hydroxy-2-(3'-nitrophenyl)pyrimidine-5-carboxylate (6 g, 21 mmol) with (chloromethylene)dimethylammonium chloride (4 g, 31 mmol) concentration of reaction mixture, followed by hexane and ether wash afford 45% of ethyl 4-chloro-2-(3'-nitrophenyl)pyrimidine-5-carboxylate, (c) reaction of ethyl 4-chloro-2-(3'-nitrophenyl)pyrimidine-5-carboxylate (1.9 g, 6 mmol) with hydrazine (0.6 g, 18 mmol) to afford 33% of ethyl 4-hydrazino-2-(3'-nitrophenyl)pyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of ethyl 4-hydrazino-2-(3'-nitrophenyl)pyrimidine-5-carboxylate (1.8 g, 6 mmol) with citraconic anhydride in analogy to Example 21, to afford 80% (0.5 g) of the title compound; m.p. 118-120°C.

Example 121

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-(4'-TRIFLUOROMETHYLPHENYL)PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) of diethyl ethoxymethylenemalonate (6.3 g, 29 mmol) with 4-trifluoromethylphenylbenzamidine (5.5 g, 29 mmol) to afford 50% of ethyl 4-hydroxy-2-(4'-trifluoromethylphenyl)pyrimidine-5-carboxylate in analogy to Example 15, (b) reaction of ethyl 4-hydroxy-2-(4'-trifluoromethylphenyl)pyrimidine-5-carboxylate (3 g, 9.6 mmol) with $POCl_3$ (49 g, 322 mmol) to afford 97% of ethyl 4-chloro-2-(4'-trifluoromethylphenyl)pyrimidine-5-carboxylate in analogy to Example 7, (c) reaction of ethyl 4-chloro-2-(4'-trifluoromethylphenyl)pyrimidine-5-carboxylate (2 g, 6 mmol) with hydrazine (0.6 g, 18 mmol) to afford 60% of ethyl 4-hydrazino-2-(4'-trifluoromethylphenyl)pyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of ethyl 4-hydrazino-2-(4'-trifluoromethylphenyl)pyrimidine-5-carboxylate (1 g, 3 mmol) with citraconic anhydride (1 g, 9 mmol) to afford 40% (0.5 g) of the title compound (m.p. 148-150°C) in analogy to Example 21.

Example 122

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-(2'-THIENYL)-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of diethyl ethoxymethylenemalonate (8 g, 35 mmol) with thienyl-2-formamidine hydrochloride (5.7 g, 35 mmol) to afford 74% of ethyl 4-hydroxy-2-(2'-thienyl)pyrimidine-5-carboxylate in analogy to Example 15, (b) reaction of ethyl 4-hydroxy-2-(2'-thienyl)pyrimidine-5-carboxylate (2 g, 8 mmol) with $POCl_3$ (24 g, 160 mmol) to afford 96% of ethyl 4-chloro-2-(2'-thienyl)pyrimidine-5-carboxylate in analogy to Example 7, (c) reaction of ethyl 4-chloro-2-(2'-thienyl pyrimidine-5-carboxylate (0.57 g, 2.2 mmol) with hydrazine (0.34 g, 11 mmol) to afford 99% of ethyl 4-hydrazino-2-(2'-thienyl)-pyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of ethyl 4-hydrazino-2-(2'-thienyl)pyrimidine-5-carboxylate (0.55 g, 2.1 mmol) with citraconic anhydride (0.71 g, 6.3 mmol) in analogy to Example 21 to afford 80% (0.61 g) of the title compound; m.p. 164-164°C.

Example 123

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)-N-METHYL]-2-(2'-THIENYL)-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) reaction of ethyl 4-chloro-2-(2'-thienylpyrimidine-5-carboxylate (0.3 g, 1.1 mmol)) with methylhydrazine (0.25 g, 5.6 mmol)) to afford 99% of ethyl 4-(1'-methylhydrazino)-2-(2'-thienyl)pyrimidine-5-carboxylate in analogy to Example 18, (b) reaction of ethyl 4-(1'-methylhydrazino)-2-(2'-thienyl)pyrimidine-5-carboxylate (0.3 g, 1 mmol)) with citraconic anhydride (0.4 g, 3 mmol) in analogy to Example 21 to afford 52% (0.21 g) of the title compound; m.p. 126-127°C.

Example 124

ETHYL 4-[N-(1'-AMINOCITRACONAMIDO)]-2-(3',4'-DICHLOROBENZYL)-PYRIMIDINE-5-CARBOXYLATE

The title compound was prepared by (a) of diethyl ethoxymethylenemalonate (6 g, 27 mmol) with 3',4'- dichlorophenylacetamidine (5.5 g, 27 mmol) to afford 37% of ethyl 4-hydroxy-2-(3',4'-dichlorobenzyl)pyrimidine-5-carboxylate in analogy to Example 15, (b) reaction of ethyl 4-hydroxy-2-(3',4'-dichlorobenzyl)pyrimidine-5-carboxylate (2 g, 6 mmol) with $POCl_3$ (14 g, 92 mmol) to afford 62% of ethyl 4-chloro-2-(3',4'-dichlorobenzyl)pyrimidine-5-carboxylate in analogy to Example 7, (c) reaction of ethyl 4-chloro-2-(3',4'-dichlorobenzyl)pyrimidine-5-carboxylate (1 g, 2.8 mmol) with hydrazine (0.27 g, 8.3 mmol) to afford 99% of ethyl 4-hydrazino-2-(3',4'-dichlorophenyl)pyrimidine-5-carboxylate in analogy to Example 18, (d) reaction of ethyl 4-hydrazino-2-(3',4'-dichlorobenzyl)pyrimidine-5-carboxylate (0.9 g, 2.7 mmol) with citraconic anhydride (0.49 g, 4.4 mmol) in analogy to Example 21 to afford 47% (0.3 g) of the title compound; m.p. 119-121°C.

Example 125

SYNTHESIS OF REPRESENTATIVE COMPOUNDS BY COMBINATORIAL CHEMISTRY TECHNIQUES

This example illustrates the synthesis of a representative class of compounds of this invention, 2-substituted-4-trifluoromethyl-5-pyrimidine carboxylic acid methyl esters, by combinatorial chemistry. It should be understood that, while a specific class of compounds are illustrated in this example, the following procedure may be employed to synthesize other compounds of this invention.

A mixture of TentaGel resin (TentaGel S PHB, Advanced Chem Tec Louisville, Kentucky, 17 g, 0.2 mmol/g reactive sites) containing a free hydroxy as the reactive site and DMF (75 mL) was stored for 0.25 h. Then a solution of 2-chloro-4-trifluoromethyl pyrimidine-5-carbonyl chloride (2.20 g, 10.2 mmol) in DMF (15 mL) was added. The mixture was gently shaken for 3 h and filtered. The resin was washed

thoroughly with DMF (3 X100 mL) and CH_2Cl_2 (3 X100 mL) and then dried under vacuum. The resin was divided into 80 equal portions and placed into 80 separate reaction vessels (dispersion tubes). The dispersion tubes were placed into separate test tubes each containing a different amine (2.5 mmol, Appendix I) and 2 mL of a 0.1M solution of pyridine/DMF (5 molar equivalents of each amine in each test tube). The entire set of 80 reaction vessels was gently shaken for 5 hours to ensure complete reaction. Then each of the dispersion tubes was removed from the test tube containing the amine and rinsed separately to remove any unreacted materials. The dispersion tubes were then dried and submersed into 80 new test tubes (previously tared), each containing a solution of NaOMe (2.5 mL, 0.012 M solution, 0.03 mmol). The reaction was allowed to proceed overnight at room temperature under N_2. Then the dispersion tubes were removed from the solution and individually rinsed with MeOH. The individual MeOH solutions were concentrated in the tared test tubes to provide known amounts of the desired 80 individual methyl esters substituted with different groups at the 2-position. Each compound was >85% pure by HPLC and had the correct molecular weight as determined by GC/MS.

Example 126

INHIBITION OF THE ACTIVATION OF NFκB AND AP-1

A. NFκB ASSAY

Stable human Jurkat T-cells containing an NFκB binding site (from the MHC promoter) fused to a minimal SV-40 promoter driving luciferase expression were used in this experiment. Cells were split to 3 x 10^5 cells/mL every 2-3 days (cell concentration should not exceed 1 x 10^6 cells/mL to keep the cells proliferating in log phase). These cells were counted, resuspended in fresh medium containing 10% Serum-Plus at a density of 1 x 10^6 cells/mL and plated in 96 well round bottom plates (200 μΛ per well) 18 hours prior to starting the experiment.

Compounds of this invention, dissolved in dimethyl sulfoxide (3.3, 0.33 and 0.03 μg/mL), were then added to the 96 well plates containing the cells and the

plates were incubated for 0.5 h at 37°C. Then 50 ng/mL of phorbol 12-myristate-13-acetate (PMA) and 1 μg/mL of phytohemagglutinin (PHA) were added to each well and the cells were incubated for an additional 5 h at 37°C. The plates were centrifuged at 2200 RPM for 3 minutes at room temperature and then the medium was removed. To each well was added 60 μL of cell lysis buffer and the plates were left at room temperature for 0.25 h. Then 40 μL of each cell extract was transferred to a black 96 well plate and 50 μL of luciferase substrate buffer was added. Luminescence was immediately measured using a Packard TopCount.

B. AP-1 ASSAY

For AP-1, the assay was run as described above for NFκB except stable Jurkat T-cells were used that contained a collagenase promoter driving luciferase expression. In addition, the concentration of PMA used was 5 ng/mL.

C. RESULTS

The results of the above assays for a representative compound of this invention, ethyl 2-[N-(1'-aminocitraconamido)]-4-pentafluoroethylpyrimidine-5-carboxylate (*see* Example 48), as percent inhibition versus control are presented in Figure 3. This figure also indicates activity of β-actin which was employed in these assays as a control cell line indicating effects on transcription. The lack of β-actin activity evidences selectivity of the test compounds for the transcription factors AP-1 and NFκB.

Expressed as IC_{50}'s, the results of these assays on additional test compounds are summarized in Table 3 below. The IC_{50} values reported in Table 3 are the average of the measurements obtained from the NFκB and AP-1 assays described above.

Table 3

Ability of Representative Compounds of Structure (I) to Inhibit NFκB and AP-1

Test Compound (Example No.)	IC_{50} (μM)	Test Compound (Example No.)	IC_{50} (μM)	Test Compound (Example No.)	IC_{50} (μM)
20	0.7	79	0.2	103	0.4
21	0.5	81	0.1	104	0.2
23	5-10	83	0.08	105	2.4
36	0.15	84	0.45	106	1.7
37	0.15	85	0.02	107	0.5
38	0.04	87	0.55	108	1.5
40	1.0	88	0.5	109	0.2
41	3.9	89	0.2	111	4.9
42	5	90	0.06	112	0.6
44	10-30	91	1.1	113	1.0
46	4.0	92	0.3	114	1.1
48	0.09	93	0.8	115	0.03
50	1.0	94	1.1	116	1.4
52	2.0	95	0.3	117	4
64	1.0	96	0.7	118	17
68	0.4	97	0.9	119	7
73	0.05	98	6.0	120	8
74	0.45	99	0.4	121	0.4
75	0.4	100	0.8	122	0.02
77	1.3	101	0.6	123	0.8
78	0.15	102	0.4	124	4

Based on the above results, representative compounds of this invention were found to be effective at inhibiting the activation of transcription factors (*i.e.*, NFκB and AP-1) involved in gene transcription, and therefore have utility as, for example, immunosuppressive agents.

Example 127

INHIBITION OF CYTOKINES

To determine the effects of compounds on PMA/PHA-induced cytokine production, supernatants from either the NFκB (for IL-8) and AP-1 (for IL-2) reporter

gene assays of Example 55 were collected and saved. Cytokine levels in the supernatants (25-50 μL aliquots) were determined by ELISA. The results of this experiment for a representative compound of this invention, ethyl 2-[N-(1'-aminocitraconamido)]-4-pentafluoroethylpyrimidine-5-carboxylate (*see* Example 48), is presented in Figure 4 (expressed as percent inhibition versus control).

Example 128

ACTIVITY OF REPRESENTATIVE COMPOUND IN GRAFT VS. HOST AND CONTACT SENSITIVITY MODELS

The murine popliteal lymph node (PLN) assay is a graft vs. host model that predicts activity of compounds in blocking human transplant rejection. The delayed-type hypersensitivity response to oxazolone is a standard contact sensitivity model. Both of these models are used routinely to evaluate compounds that are used clinically. For example, cyclosporin and cyclophosphamide are active in these models and are used clinically (Morris et al., *Transplantation Proceedings* **22**(Suppl. 1):110-112, 1990).

A. POPLITEAL LYMPH NODE MODEL

Spleens are removed from donor BALB/c mice and splenocytes are isolated then irradiated (3,000 rads) to prevent donor cell proliferation. After washing and adjusting cell density, 2.5×10^6 cells are injected subcutaneously into the left hind footpad of C3H mice. On day 4, the mice are sacrificed and left popliteal lymph nodes (PLNs) weighed.

A representative compound of this invention is administered once daily by intraperitoneal injection beginning one day before footpad injection (day 0) through day 4. The compound is suspended, immediately prior to use, at a concentration of 5 mg/mL in 0.25% methyl cellulose (Sigma) using a glass-Teflon homogenizer. For doses of 10, 20 and 30 mg/kg, appropriate dilutions of the stock solution are made so that 0.1 mL/10 g body weight is administered by intraperitoneal injection.

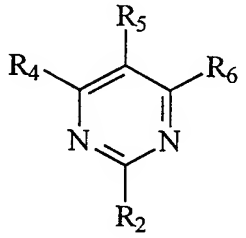
B. DELAYED TYPE HYPERSENSITIVITY STUDY

On day 0, oxazolone (100 mL of a 3% solution) is applied to the shaved abdomen of mice. On day 7, a challenge application of oxazolone is applied (10 mL) around the right ear. A representative compound of this invention is administered from days -2 to 7 by intraperitoneal injection. The injectable solution is prepared immediately prior to use by suspending the compound in 0.25% methyl cellulose (Sigma) using a glass-Teflon homogenizer. For each dose, 0.1 mL/10 g body weight of the suspension is administered. The compound is prepared at the highest concentration for this study and appropriate dilutions of the stock solution are made so that 0.1 mL/10 g body weight is administered. Twenty four hours later, the difference in right vs. left ear thickness is measured.

It will be appreciated that, although specific embodiments of this invention have been described herein for purpose of illustration, various modifications may be made without departing from the spirit and scope of the invention.

Claims

1. A compound having the structure:

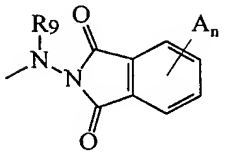


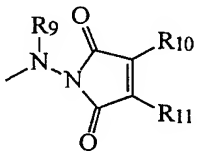
including pharmaceutically and prophylactically acceptable salts thereof, wherein

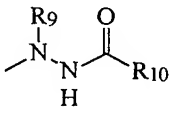
R_2 is R_{2a} when R_4 is R_{4a}, and R_2 is R_{2b} when R_4 is R_{4b};

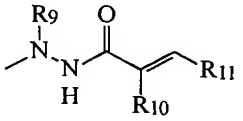
R_{2b} and R_{4a} are selected from hydrogen, halogen and an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl;

R_{2a} and R_{4b} are selected from the following chemical moieties:









R_5 is selected from $-CH_2O\{C(=O)O\}_{0,1}R_7$, $-C(=O)OR_7$ and $-C(=O)R_8$;

R_6 is selected from hydrogen, $-CH_3$, $-CH_2C_6H_5$, -F and $-CF_3$;

R_7 is selected from hydrogen and a unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl and C_{7-12}aralkyl;

R_8 is an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl;

R_9 is selected from hydrogen -C(=O)-D-R_7 and an unsubstituted C_{1-8}alkyl or C_{7-14}aralkyl, wherein D is a direct bond, -O- or -NH-;

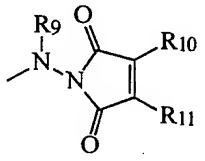
R_{10} and R_{11} are the same or different and independently selected from hydrogen and an unsubstituted or substituted C_{1-8}alkyl or C_{6-12}aryl; and

n is an integer from 0 to 4 and each occurrence of A is a substituent independently selected from halogen, -OH, -R, -OR, -COOH, -COOR, -COR, $-CONH_2$,

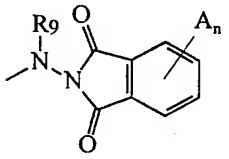
-NH_2, -NHR, -NRR, NO_2, -SH, -SR, -SOOR, -SO_3R and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl or C_{7-12}aralkyl.

2. The compound of claim 1 wherein R_2 is R_{2a}, R_4 is R_{4a}, and R_5 is -C(=O)OR_7.

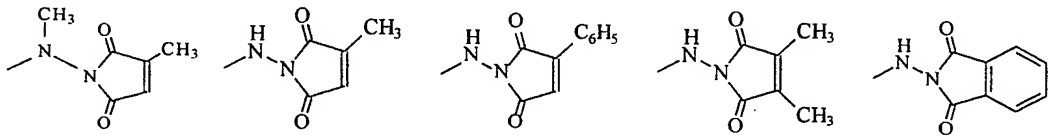
3. The compound of claim 2 wherein R_{2a} is selected from one of the following structures:



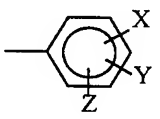
and



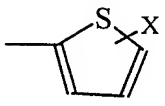
4. The compound of claim 2 wherein R_{2a} is selected from one of the following structures:



5. The compound of claim 2 wherein R_{4a} is selected from -Cl, -CF_3, -CH_3, -$(CH_2)_{1-2}CH_3$, -C_2F_3,



and



wherein X, Y and Z are the same or different, and independently selected from hydrogen, -OH, -R, -OR, -COOH, -COOR, -COR -$CONH_2$, -NH_2, -NHR, -NRR, -NO_2, -SH,

-SR, -SOOR, -SO_3R and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl.

6. The compound of claim 2 wherein R_6 is selected from hydrogen, -CF_3 and -CH_3.

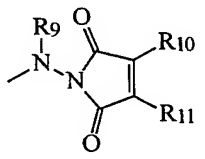
7. The compound of claim 2 wherein R_7 is selected from hydrogen, -CH_3 and -CH_2CH_3.

8. The compound of claim 2 wherein R_9 is selected from hydrogen, -CH_3, -CH_2CH_3 and -$CH_2C_6H_5$.

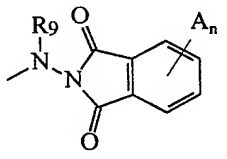
9. The compound of claim 2 wherein R_{10} and R_{11} are independently selected from hydrogen, -CH_3, -CF_3, -$(CH_2)_{1-5}CH_3$, -C_6H_5 and -$CH_2C_6H_5$.

10. The compound of claim 1 wherein R_2 is R_{2b}, R_4 is R_{4b}, and R_5 is -C(=O)OR_7.

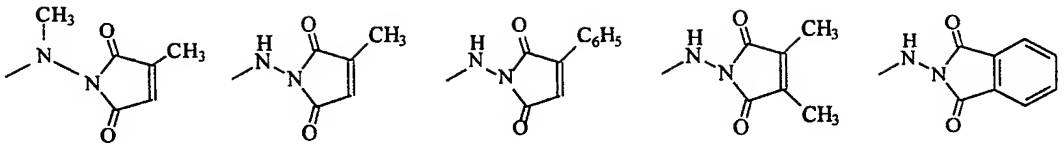
11. The compound of claim 10 wherein R_{4b} is selected from one of the following structures:



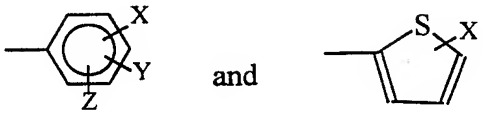
and



12. The compound of claim 10 wherein R_{4b} is selected from one of the following structures:



13. The compound of claim 10 wherein R_{2b} is selected from -Cl, $-CF_3$, $-CH_3$, $-C_6H_5$, $-(CH_2)_{1-2}CH_3$, $-C_2F_3$,



wherein X, Y and Z are the same or different, and independently selected from hydrogen, -OH, -R, -OR, -COOH, -COOR, -COR, $-CONH_2$, $-NH_2$, -NHR, -NRR, $-NO_2$, -SH, -SR, -SOOR, $-SO_3R$ and -SOR, where each occurrence of R is independently selected from an unsubstituted or substituted C_{1-8}alkyl, C_{6-12}aryl, C_{7-12}aralkyl, C_{3-12}heterocycle or C_{4-16}heterocyclealkyl.

14. The compound of claim 10 wherein R_6 is selected from hydrogen, $-CF_3$ and $-CH_3$.

15. The compound of claim 10 wherein R_7 is selected from hydrogen, $-CH_3$ and $-CH_2CH_3$.

16. The compound of claim 10 wherein R_9 is selected from hydrogen, $-CH_3$, $-CH_2CH_3$ and $-CH_2C_6H_5$.

17. The compound of claim 10 wherein R_{10} and R_{11} are independently selected from hydrogen, $-CH_3$, $-CF_3$, $-(CH_2)_{1-5}CH_3$, $-C_6H_5$ and $-CH_2C_6H_5$.

18. The compound of claim 1 wherein the compound is selected from ethyl 2-(N-(1'-aminocitraconamido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminophthalimide))-4-trifluoromethylpyrimidine-5-carboxylate; 5-acetyl-2-(N-(1'-aminocitraconamido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-amino-3'-phenylmaleimido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-amino-3',4'-dimethylmaleimido))-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-trifluoromethylpyrimidine-5-carboxylate; ethyl 4-(N-(1'-amino-3'-phenylmaleimido))-2-trifluoromethylpyrimidine-5-carboxylate; ethyl 4-(N-(1'-amino-3', 4'-dimethylmaleimido))-2-trifluoromethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-methylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-pentafluoroethylpyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-phenylpyrimidine-5-carboxylate; methyl 2-(N-(1'-aminocitraconamido))-4-(3'-pyridyl)pyrimidine-5-carboxylate; diethyl 2-(N-(1'-aminocitraconamido))pyrimidine-4,5-dicarboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-ethylpyrimidine-5-carboxylate; methyl 2-(N-(1'-aminocitraconamido))-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido)-N-methyl)-4-(2'-thienyl)pyrimidine-5-carboxylate; ethyl 2-(N-(1'-aminocitraconamido))-4-(5'-methyl-2'-thienyl)pyrimidine-5-carboxylate; ethyl 4-(N-(1'-aminocitraconamido))-2-phenylpyrimidine-5-carboxylate; and ethyl 4-(N-(1'-aminocitraconamido))-2-(2'-thienyl)pyrimidine-5-carboxylate.

19. A composition comprising a compound of claims 1-18 and a pharmaceutically or prophylactically acceptable carrier or diluent.

20. Use of a compound of claims 1-18 as an active therapeutic substance.

21. Use of a compound of claims 1-18 for the manufacture of a medicament for treating an inflammatory condition.

22. The use of claim 21 wherein the inflammatory condition is an immunoinflammatory condition.

23. The use of claim 22 wherein the immunoinflammatory condition is selected from rheumatoid arthritis, osteoarthritis, transplant rejection, sepsis, ARDS and asthma.

24. The use of claim 22 wherein the immunoinflammatory condition is rheumatoid arthritis.

25. The use of claim 21 wherein the inflammatory condition is an autoimmune disease.

26. The use of claim 25 wherein the autoimmune disease is selected from multiple sclerosis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis and chronic hepatitis.

27. The use of claim 21 wherein the inflammatory condition is selected from trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer and viral infection.

28. The use of claim 21 wherein the inflammatory condition is transplant rejection.

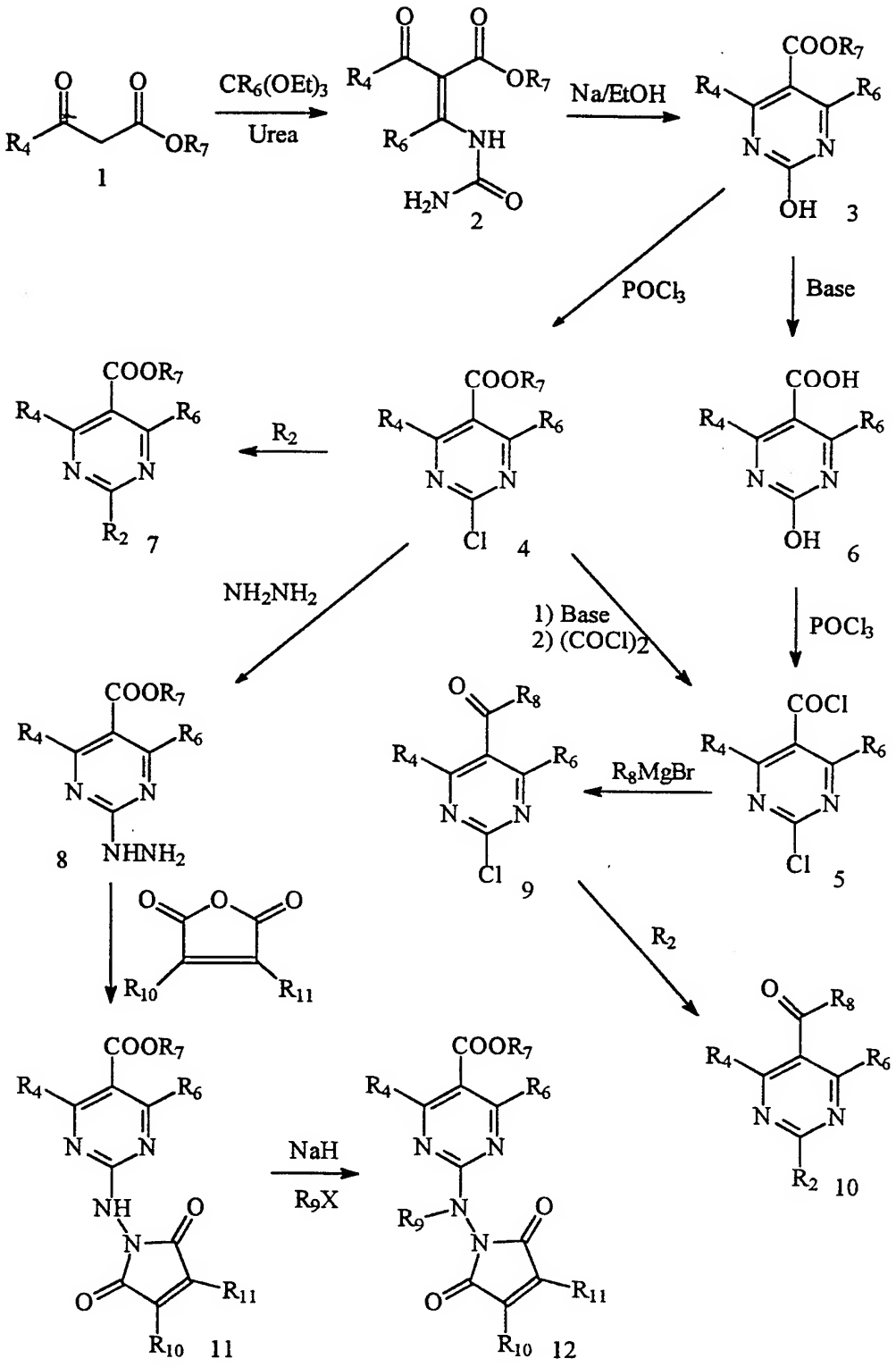

CR6(OEt)3
Urea
Na/EtOH
POCl3
Base
R2
NH2NH2
1) Base
2) (COCl)2
R8MgBr
NaH
R9X
1
2
3
4
5
6
7
8
9
10
11
12

Figure 1

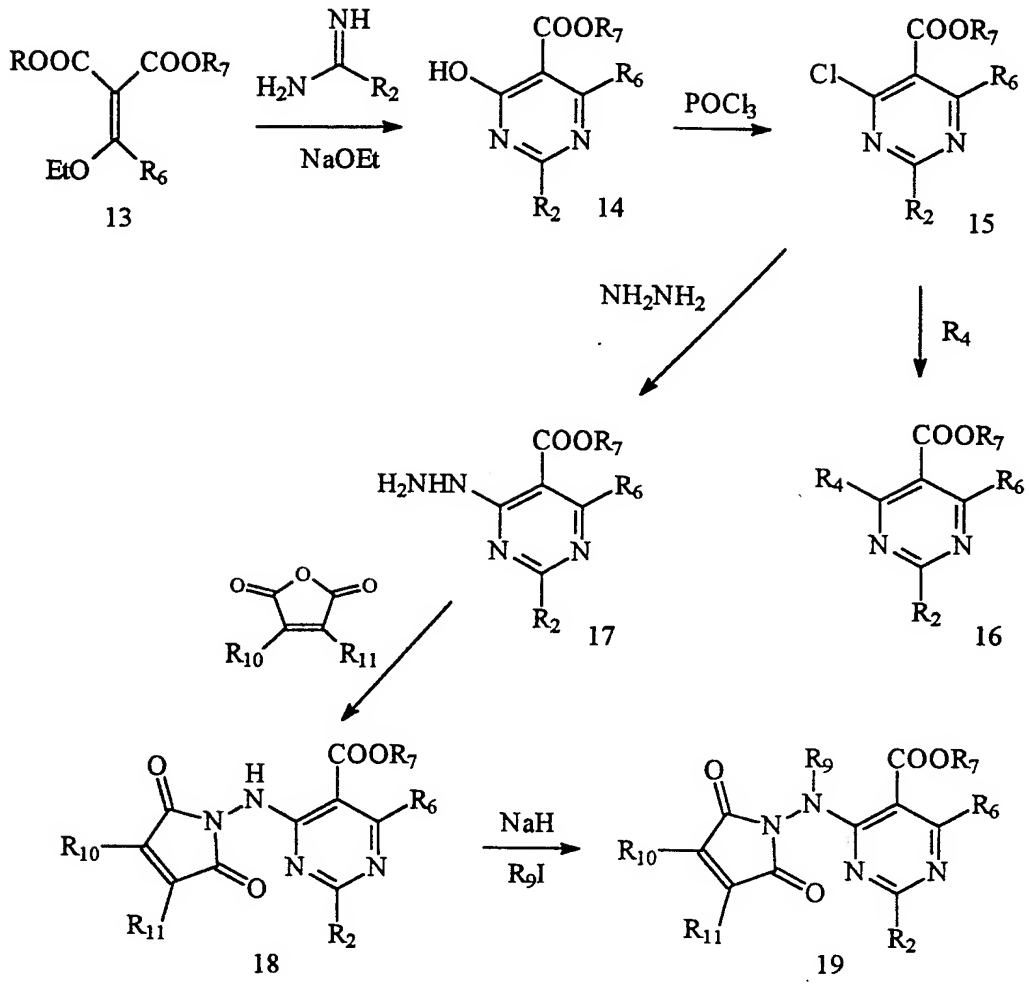

ROOC
COOR7
EtO
R6
13
NH
H2N
R2
NaOEt
HO
COOR7
R6
N
N
R2
14
POCl3
Cl
COOR7
R6
N
N
R2
15
NH2NH2
R4
H2NHN
COOR7
R6
N
N
R2
17
R4
COOR7
R6
N
N
R2
16
O
O
O
R10
R11
O
H
N
N
COOR7
R6
R10
N
N
O
R11
R2
18
NaH
R9I
R9
N
19

Figure 2

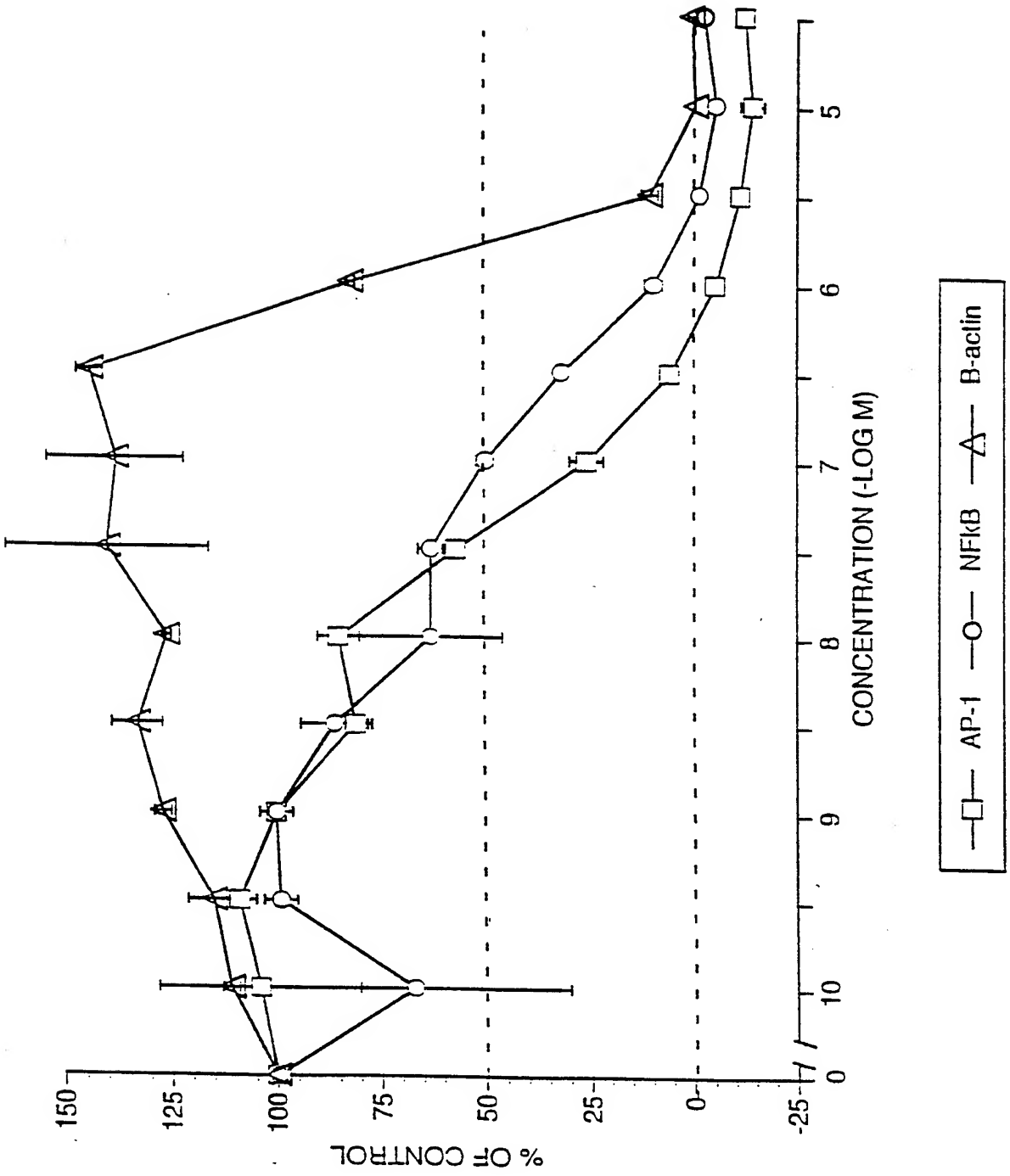

% OF CONTROL
150
125
100
75
50
25
0
-25
0
5
6
7
8
9
10
CONCENTRATION (-LOG M)
AP-1
NFkB
B-aclin

Figure 3

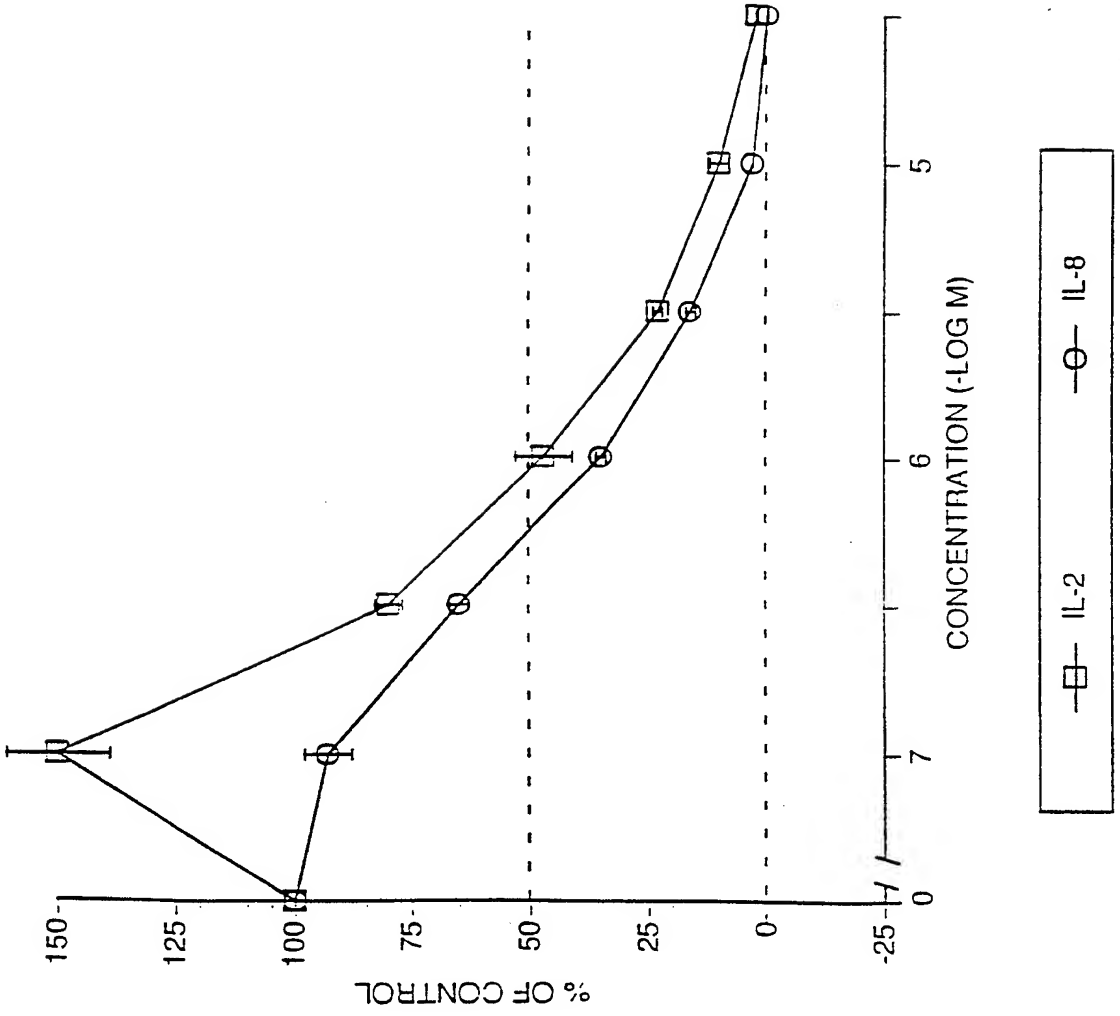

% OF CONTROL
150
125
100
75
50
25
0
-25
0
5
6
7
CONCENTRATION (-LOG M)
IL-2
IL-8

Figure 4

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/14089

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/12 C07D239/42 C07D409/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 983 608 (R.EFFLAND) 8 January 1991 see column 1 - column 19	1,19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 1996	20. 12. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...nformation on patent family members

Inter ...nal Application No
PCT/US 96/14089

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4983608	08-01-91	AU-B-	626450	30-07-92
		AU-A-	6208990	14-03-91
		CA-A-	2024572	06-03-91
		EP-A-	0417584	20-03-91
		IL-A-	95568	24-01-95
		JP-A-	3093784	18-04-91
		JP-B-	7116181	13-12-95
		US-A-	5179204	12-01-93